The Role of Occupational Exposure on Chronic Obstructive Pulmonary Disease in Middle-aged Adults

Sheikh Mohammad Alif
BDS, MPH

ORCID ID: 0000-0002-0783-8848

Submitted in total fulfilment of the requirements of the degree of
Doctor of Philosophy

August 2017

Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics
Melbourne School of Population and Global Health
Faculty of Medicine, Dentistry and Health Sciences
The University of Melbourne

Dedication

This thesis is dedicated to my beloved family

Thesis abstract

Background: Chronic Obstructive Pulmonary Disease (COPD) contributes significantly to the global burden of disease. COPD is characterized by the presence of fixed airflow obstruction (AO) as measured by spirometry and defined by irreversible reduction in the post-bronchodilator (BD) ratio between the forced expiratory volume in one second and forced vital capacity (FEV_1/FVC). Chronic bronchitis, chronic respiratory symptoms and lung function decline over time are also significant predictors of COPD. However, they are also considered separate conditions as these may exist with normal lung function. Smoking is the main risk factor for COPD but a large number of people with COPD are never smokers, so other factors are contributing to the disease burden. Occupational exposure is one of the known important preventable risk factor for this disease. Understanding how occupational exposures contribute to the overall risk of COPD in the general population is essential to be able to gain a greater understanding of COPD etiology and to be able to identify high-risk occupational groups. Population-based studies have found evidence of a relationship between some occupational exposures and COPD. However, a critical review of literature presented in Chapter 2, identified that studies to date investigating these relationships have had some significant limitations including lack of post-BD measurement, limited use of lifetime work history and cumulative exposure assessment. Furthermore, some common occupational exposures with known respiratory impacts have not been investigated in relation to fixed AO with adequate consideration of asthma and lung function decline. Therefore, the aim of my doctoral work was to investigate the effects of occupational exposures on COPD using robust definitions of COPD, chronic bronchitis, and lung function decline and to explore if any effect modification existed.

My systematic review and meta-analyses (Chapter 3) identified an association between low exposure to mineral dust and high exposure to gases/fumes and COPD, and both low and high exposure to biological dust and mineral dust were associated with

chronic bronchitis. This work further helped to identify some of the major gaps in the literature that I have addressed in my subsequent analysis.

Methods: In Chapter 4, I used data from the population-based Tasmanian Longitudinal Health Study (TAHS). Lifetime work history calendars were collected at age 45 years, and occupational exposures were assigned using the ALOHA plus Job Exposure Matrix and defined as ever exposed and cumulative exposure-unit years. Multivariable linear and logistic regressions were used to investigate the associations adjusting for possible confounders.

Results: In Chapter 5, I examined the associations between occupational exposure and COPD defined by fixed AO, chronic bronchitis, and respiratory symptoms. I found consistent significant associations between ever exposure and cumulative exposure-unit years to pesticides and herbicides and fixed AO, chronic bronchitis, and respiratory symptoms. I also found evidence of effect modification by current asthma for the association between biological dust, mineral dust, and gases/fumes and fixed AO.

In Chapter 6, I examined the association between exposure to solvents and metals and COPD as defined by fixed AO and gas transfer factor. I found an association between ever exposure to metals and fixed AO. Interestingly I also found an association between increasing cumulative exposure-unit years to chlorinated solvents and fixed AO and fixed AO plus low $D_L$co but only in women, not in men.

In Chapter 7, I investigated the association between occupational exposures and lung function decline between age 45 and 50 years. I found an association between both ever exposure and cumulative exposure-unit years to aromatic solvents and a greater decline in lung function. I also found that increasing cumulative exposure-unit years to aromatic solvents were associated with a greater lung function decline in women, but not in men.

Conclusions: Collectively these findings have strengthened and have filled some major gaps in our understanding of the links between overall occupational exposure and the development of COPD in an adult population. I have confirmed in my study that exposure to pesticides is a risk factor for COPD with solvents and metals exposure also linked to an increased risk of COPD. Importantly, my findings suggest that women are at a greater risk of COPD when exposed to solvents. These findings lead me to make several important public health recommendations. Firstly, workplaces need to be monitored to ensure exposure to pesticides and solvents is reduced via adequate ventilation, storage, and usage solutions. Secondly, occupational groups with regular and high exposure to these chemicals need to be encouraged to utilize personal protective equipment, together with routine monitoring. By implementation of these control measures, the burden of COPD caused by occupational exposures has the potential to be reduced.

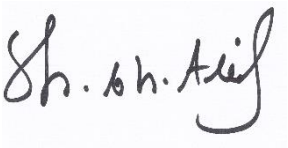
Declaration

This is to certify that

I. The thesis comprises only my original work towards the PhD, except where indicated in the acknowledgements.

II. Due acknowledgment has been made in the text to all other material used.

III. The thesis is less than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.



…….

Sheikh Mohammad Alif

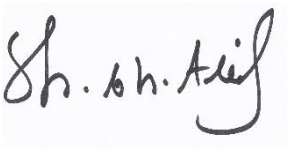
19/08/2017

Preface

I have included three published first author papers with multiple co- authors as a results chapter (Chapter 3, Chapter 5 and Chapter 6) in this thesis.

I drafted all the included publications in this thesis and incorporated all critical reviews from the co-authors. I also performed literature review, cleaned and prepared the dataset for analysis and finally performed the statistical analyses in each of the included papers. I also revised the submitted manuscript by addressing reviewer comments. Other co-authors of the papers provided assistance with the data collection and analytical design, interpretation of the results, and critically reviewed the drafted manuscript. As such, signed collaborator authorization forms have been provided by each co-author of published manuscripts, as well as a declaration of collaborative work from my principal supervisor are submitted to the Melbourne School of Graduate Research. All the work included in this thesis was carried out after my enrolment as a higher research degree student.

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.



……..

Sheikh Mohammad Alif
The University of Melbourne
Victoria, Melbourne, Australia

Acknowledgements

First and foremost, I would like to acknowledge my principal supervisor Associate Professor Melanie Matheson for giving me the opportunity to embark on this journey and challenge my limits while continuing to support me throughout this remarkable journey. Her mentorship, understanding, encouragement, patience and calming influence have immensely helped me to remain focused in the last four years. I am also grateful to my co-supervisor and principal investigator of the TAHS study since 2002, Professor Shyamali Dharmage for her guidance, support, and critical feedback throughout my PhD candidature. My sincere thanks go to all my other co-supervisors' Dr Geza Benke and Dr Martine Dennekamp for their inputs with analytical designs and manuscript writing during my PhD candidature. I would also like to thank my advisory panel, Professor Mark Jenkins and Dr Ryan Hoy for their contribution and support over the last four years.

I was incredibly fortunate to work with such a great and diverse Allergy and Lung Health research group and a team with friendly and supportive higher research degree students and research fellows. In particular, I would like to acknowledge Dr Jennifer Perret and Dr John Burgess for always being very helpful. I would like to thank my friends and fellow doctoral students, particularly Dr Gayan Bowatte, Dinh Bui, Melisa Lau, Dr Rachel Tham, Alison Yates, Geoff Browne, Dr Shahid Mahmood, Dr Farhana Sultana, and Sabria Jihan Khan for their support and importantly, for giving me a friendly environment out of my PhD life.

I acknowledge the founders of the TAHS in 1968 (H. Gibson, B. Gandevia and H. Silverstone) as well as all the current and past TAHS investigators. I would also like to acknowledge all the funding bodies that supported follow ups of both cohorts including the Australian National Health and Medical Research Council. The contribution of many co-authors has been acknowledged in the publications, in particular, Professor Michael Abramson, Professor Haydn Walters, and Professor David Johns.

I would like to sincerely thank the University of Melbourne for providing me with the Melbourne International Research Scholarship (MIRS), and Melbourne International Fee Remission Scholarship (MIFRS). I also thank Melbourne School of Population and Global Health for awarding me Public Health Initiative for Research Student Training (PHIRST) travel grants to attend conferences of Thoracic Society of Australia and New Zealand in 2015 and 2016. I would like to acknowledge my principal supervisor Associate Professor Melanie Matheson for extending the financial support and providing me the opportunity to work with TAHS after finishing my scholarship allowances, particularly after three and half years of my PhD.

Finally, I would like to thank my lovely responsible mom, Mrs Merin Sultana who did many sacrifices for me, guided and encouraged me in every step in my life, particularly in difficult times. I also would like to acknowledge my dad; Mohammad Hanif his suggestion always helped me to keep myself focus on my PhD. I am especially thankful to my dad for his continuous financial support for my education and for providing this financial support during my PhD life as well. My six and half-year-old daughter Aleena Firdous has shown a lot of maturity and endurance that helped me enormously to keep my concentration in my PhD. Last and most importantly, I am grateful to my beloved wife Dr Naima Nimmi for her understanding and constant support that helps me to take the proper decision in my PhD life and without her sacrifice, love and support I would not have come this far to complete my PhD.

Achievements

Awards (September 2013-August 2017)

1) International Trainee Scholarship, American Thoracic Society (ATS), 2016 International conference, San Francisco, California, United States of America.
2) Abstract Scholarship: Assembly on Environmental and Occupational Population Health (EOPH), ATS 2016 International conference, San Francisco, California, United States of America.
3) Travel Award: The Thoracic Society of Australia and New Zealand (TSANZ), Perth, Western Australia, 2016.
4) Travel Award: Public Health Initiative for Research Student Training (PHIRST), Higher Degree by Research Funding Scheme, Melbourne School of Population and Global Health, 2015.
5) Best oral presentation award: The Thoracic Society of Australia and New Zealand Victorian Branch Meeting, 2015.
6) Travel Award: The Thoracic Society of Australia and New Zealand (TSANZ), Gold Coast, Queensland, 2014.
7) PhD Scholarships, Melbourne International Research Scholarships, The University of Melbourne, 2013-2017

Publications (September 2013-August 2017)

First author peer-reviewed publications arising from this thesis:

Alif S, Dharmage S, Bowatte G, Karahalios A, Benke G, Dennekamp M, Mehta A, Miedinger D, Künzli N, Hensch N, Matheson M.

"Occupational exposure and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analysis."

Expert Rev Respir Med 2016; 10 (8): 861-872.

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret J, Lodge C, Morrison S, Johns D, Giles G, Gurrin L, Thomas P, Hopper J, Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Walters E, Abramson M, Matheson M.
"Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age."
Thorax 2017 (In press).

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret J, Lodge C, Morrison S, Johns D, Giles G, Gurrin L, Thomas P, Hopper J, Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Walters E, Abramson M, Matheson M.
"Occupational exposure to solvents and metals are associated with fixed airflow obstruction."
Scand J Work Environ Health 2017 (In press)

Under review/submitted

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret J, Lodge C, Morrison S, Johns D, Giles G, Gurrin L, Thomas P, Hopper J, Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Garcia-Aymerich J, Jarvis D, Walters H, Abramson M, Matheson M.
"Occupational exposures and lung function decline."
(submitted to American Journal of Respiratory and Critical Care Medicine)

Conference abstracts

Alif S, Dharmage S, Karahalios A, Bowatte G, Benke G, Dennekamp M, Matheson M.
"Occupational exposures and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analyses."
Respirology 2015; 20 (Suppl 2): 75, TP035.
The Thoracic Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting 2015. Gold Coast, Queensland, Australia **(Poster presentation)**

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret J, Lodge C, Morrison S, Johns D, Giles G, Thomas P, Vermeulen R, Kromhout H, Abramson M, Walters E, Matheson M.

"Occupational exposure to vapour, gases/fumes, dust and lung function in middle-aged population."

Respirology; 2016; 21(Suppl 2): 95 TP146.

The Thoracic Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting 2016. Perth, Western Australia, Australia **(Oral presentation)**

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret J, Lodge C, Morrison S, Johns D, Giles G, Thomas P, Vermeulen R, Kromhout H, Abramson M, Walters E, Matheson M.

"Lifetime occupational exposure to vapor, gases/fumes, dust and risk of COPD at 45 years: the Tasmanian Longitudinal Health Study (TAHS)."

Am J Respir Crit Care Med; 2016; 193: A2989.

American Thoracic Society Annual Conference 2016. San Francisco, California, USA **(Poster presentation)**

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret J, Lodge C, Morrison S, Johns D, Giles G, Gurrin L, Thomas P, Hopper J, Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Walters E, Abramson M, Matheson M.

"Occupational exposure to solvents and metals are associated with fixed airflow obstruction."

(Accepted for "**oral presentation**" in the Congress of Asian Pacific Society of Respirology 2017)

In addition, I have had 15 presentations at the Allergy and Lung Health Unit, Melbourne School of Population and Global Health weekly seminars in the last four years. I also presented at Melbourne School of Population and Global Health Student Conference in 2015 and Australian Society for Medical Research (ASMR) Victorian

Student Research Symposium in 2016.

Invited reviewer/chair

Alif S, Invited reviewer of manuscripts for the Expert Review of Respiratory Medicine, November 2015 and February 2016

Alif S, Invited abstract reviewer for the Thoracic Society of Australia and New Zealand (TSANZ) Annual Scientific Meeting 2017. Canberra, Australian Capital Territory, Australia.

Alif S, Invited chair for oral presentation on occupational epidemiology, 29th Annual Scientific Conference of the International Society of Environmental Epidemiology (ISEE 2017) in Sydney, Australia.

Training and courses

Coursework subjects training for graduate researchers; epidemiology, biostatistics, linear and logistic regression, survival analysis and regression for rates.

Training in the statistical software Stata from the clinical epidemiology and biostatistics unit at the Murdoch Children's Research Institute, The Royal Children's Hospital, Melbourne, Australia.

Attended several UpSkills courses at the University of Melbourne on statistics and academic writing.

Abbreviations

AO	Airflow Obstruction
ALOHA	A Lot of Occupational Hygienist Assumptions
ATS	American Thoracic Society
AIHW	Australian Institute of Health and Welfare
BHR	Bronchial Hyper-responsiveness
BD	Bronchodilator
BOLD	Burden of Obstructive Lung Disease
COPD	Chronic Obstructive Pulmonary Disease
CB	Chronic Bronchitis
CMH	Chronic Mucus Hyperresponsiveness
CI	Confidence Interval
CNSLD	Chronic Non-Specific Lung Disease
D_Lco	Diffusing capacity of the lung for carbon monoxide
DAG	Directed Acyclic Graph
ERS	European Respiratory Society
ECRHS	European Community Respiratory Health Survey
ETS	Environmental Tobacco Smoke
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
FEF	Forced Expiratory Flow
FIOH	Finnish Institute of Occupational Health
FFHHSP	Farm Family Health and Hazard Surveillance Program
EU	Exposure Unit
FINJEM	Finnish Job Exposure Matrix
GOLD	Global Obstructive Lung Disease
GLI	Global Lung Initiative
HIC	Health Insurance Commission

ISCO	International Standard Classification of Occupations
ISCED	International Standard Classification of Education
IQR	Interquartile Range
JEM	Job Exposure Matrix
JEMs	Job Exposure Matrices
LLN	Lower Limit of Normal
LF	Lung Function
NHANES	National Health and Nutrition Examination Survey
NDI	National Death Index
OR	Odds Ratio
PhD	Doctor of Philosophy
PLATINO	Latin American Project for the Investigation of Obstructive Lung Disease
RR	Relative Risk
SAPALDIA	Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults
SR	Self-Reported
SD	Standard Deviation
SES	Socioeconomic Status
SPTs	Skin Prick Testing
SEIFA	Socio-Economic Indexes for Areas
TAHS	Tasmanian Longitudinal Health Study
TSANZ	Thoracic Society of Australia and New Zealand
T_LCO	Carbon Monoxide Lung Transfer Factor
TRA	Twin Research Australia
USA	United States of America
UK	United Kingdom
VDGF	Vapour, Dust, Gases and Fumes
WHC	Work History Calendar
WHO	World Health Organization

Table of Contents

Thesis abstract ..... **v**
Declaration ..... **viii**
Preface ..... **ix**
Acknowledgements ..... **x**
Achievements ..... **xii**
Abbreviations ..... **xvi**
Table of Contents ..... **xviii**
List of Tables ..... **xxiii**
List of Figures ..... **xxv**
Chapter 1 Introduction **1**
1.1 Rationale 3
1.1.1 Overall context of my doctoral work 4
1.2 Main Objectives 5
1.2.1 Thesis statement 6
1.2.2 Thesis overview 6
Chapter 2 Literature review **7**
2.1 Global burden of COPD 9
2.1.1 Global prevalence of COPD 9
2.1.2 Global COPD mortality 10
2.1.3 Burden of COPD in Australia 11
2.2 Definitions of COPD 12
2.2.1 Spirometry and FEV_1 cut-off point to define COPD 12
2.3 Risk factors for COPD 14
2.3.1 Extrinsic risk factors 14
2.3.2 Intrinsic risk factors 15
2.3.3 Other risk factors 16
2.4 Occupational exposures as a risk factor for COPD 17
2.4.1 Biological impact of occupational exposure on the respiratory tract 17
2.4.2 Population-based versus workplace-based studies 18

2.4.3 Assessment of occupational exposure in the general population 19
2.5 Lifetime occupational exposure versus current job exposure 25
2.6 The association between occupational exposures, and respiratory symptoms, chronic bronchitis, and COPD 28
2.6.1 Biological dust exposure 28
2.6.2 Mineral dust exposure 35
2.6.3 Gases/fumes exposure 42
2.6.4 Pesticides exposure 48
2.6.5 Solvents exposure 55
2.6.6 Heavy metals exposure 63
2.7 Association between occupational exposures and lung function decline 68
2.8 Influence of sex on occupational exposure and COPD 71
2.9 Summary of knowledge gaps in the current literature 72
Chapter 3 Occupational exposure and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analysis 75
3.1 Chapter introduction 77
3.2 Research questions and aims 77
3.2.1 Research question 77
3.2.2 Research aims 77
3.3 Publication 77
3.3.1 Main document 77
Chapter 4 Methods 91
4.1 Study design 93
4.2 Study sample and data collection 96
4.2.1 The TAHS baseline study in 1968 96
4.2.2 The TAHS 1974 follow-up study 97
4.2.3 Proband 2002 to 2008 follow-up study 97
4.2.4 Proband 2010 to 2012 follow-up study 99
4.3 Lung function measurements 100
4.3.1 Lung function in proband 2002 to 2008 clinical study 100

4.3.2 Lung function and methacholine challenge test in proband 2010 to 2012 clinical study 101
4.4 TAHS Lifetime Work History Calendars data and occupational exposure 101
4.4.1 Lifetime Work History Calendars 101
4.4.2 Job coding 102
4.4.3 Occupational exposure assessment 105
4.4.4 Cumulative exposure-unit years calculation 107
4.5 Definitions of the main outcomes 108
4.5.1 Categorical lung function and respiratory symptoms 108
4.5.2 Continuous lung function 108
4.5.3 Confounders 109
4.6 Statistical analyses 110
4.7 Ethics 111
Chapter 5 Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age 113
5.1 Chapter introduction 115
5.2 Research questions and aims 115
5.2.1 Research questions 115
5.2.2 Aims 115
5.3 Publication 115
5.3.1 Main document and online data supplement 115
Chapter 6 Occupational exposure to solvents and metals are associated with fixed airflow obstruction 135
6.1 Chapter introduction 137
6.2 Research questions and aims 137
6.2.1 Research questions 137
6.2.2 Aims 137
6.3 Publication 137
6.3.1 Main document and online data supplement 137
Chapter 7 Occupational exposures and lung function decline 157

7.1 Chapter abstract 159
7.2 Chapter introduction 160
7.3 Research questions and aims 161
7.3.1 Research questions 161
7.3.2 Aims 161
7.4 Methods 161
7.4.1 Study design 161
7.4.2 Lung function measurements 163
7.4.3 Occupational exposures 163
7.4.4 Definitions of confounders 163
7.4.5 Statistical analyses 164
7.5 Results 165
7.5.1 Population characteristics 165
7.5.2 Prevalence of occupational exposures 166
7.5.3 Ever exposure to occupational exposures and lung function decline 166
7.5.4 Cumulative exposure-unit-years and lung function decline 169
7.5.5 Effect modification 170
7.6 Chapter discussion 174
Chapter 8 Overall discussion 179
8.1 Thesis summary 181
8.2 Chapter 3- summary 181
8.3 Chapter 5- summary 182
8.4 Chapter 6- summary 183
8.5 Chapter 7- summary 184
8.6 Study strengths and limitations 186
8.6.1 Study design 186
8.6.2 Occupational exposure assessment 187
8.6.3 Definitions of COPD and lung function 188
8.6.4 Confounding variables 190
8.7 Association or causation 191
Chapter 9 Recommendations and conclusions 195

9.1 Recommendations 197
9.1.1 Clinical recommendations 197
9.1.2 Public health recommendations 198
9.1.3 Research recommendations and future directions 201
9.2 Conclusions 202
References 205
Appendices 227
Appendix 1- The TAHS 1968 baseline study questionnaire 229
Appendix 2- The TAHS 2002 follow-up postal survey questionnaire 233
Appendix 3- The TAHS 2004 laboratory study questionnaire 244
Appendix 4- The TAHS 2005 laboratory follow-up clinical testing 266
Appendix 5- The TAHS 2002-2008 follow-up lifetime work history calendar 274
Appendix 6- The TAHS 2010 follow-up postal survey questionnaire 276
Appendix 7- The TAHS 2010 follow-up laboratory questionnaire 287
Appendix 8- Reports on Reuters Health 316

List of Tables

Table 2.1 Industries with biological dust inhalation hazards..... 29

Table 2.2: Population-based studies investigating the association between biological dust exposure and respiratory symptoms and chronic bronchitis..... 31

Table 2.3: Population-based studies investigating the association between biological dust exposure and COPD..... 34

Table 2.4: Industries with mineral dust exposure..... 36

Table 2.5: Population-based studies investigating the association between mineral dust and respiratory symptoms and chronic bronchitis..... 39

Table 2.6: Population-based studies investigating the association between mineral dust exposure and COPD..... 41

Table 2.7: Population-based studies investigating the association between gases/fumes exposure with respiratory symptoms and chronic bronchitis..... 44

Table 2.8: Population-based studies investigating the association between gases/fumes exposure and COPD..... 47

Table 2.9: Commonly used pesticides and their chemical name..... 49

Table 2.10: Workplace-based studies investigating the association between pesticides exposure and respiratory symptoms and chronic bronchitis..... 52

Table 2.11: Population-based studies investigating the association between pesticide exposures and COPD..... 54

Table 2.12: Solvents (organic) families..... 57

Table 2.13: Population-based studies investigating the association between solvents (organic) exposure and respiratory symptoms and chronic bronchitis..... 60

Table 2.14: Population-based studies investigating the association between solvents (organic) exposure and COPD 62

Table 2.15: Population-based studies investigated the association between metals exposure with respiratory symptoms and chronic bronchitis 65

Table 2.16: Population-based studies investigating the association between metals exposure and COPD 67

Table 2.17: Longitudinal population-based studies investigating the association between occupational exposure and lung function decline 70

Table 4.1 ISCO-88 occupational classifications 104

Table 4.2 An example of ALOHA plus JEM based occupational classification 106

Table 7.1 Study characteristic and lung function 165

Table 7.2 Prevalence of occupational exposures 166

Table 7.3 Associations between ever exposures to dust and solvents and declines in lung function 168

Table 7.4 Associations between ever exposures to pesticides and decline in lung function 169

Table 7.5 Association between cumulative EU-years and declines in lung function 170

Table 7.6 Effect modification by sex on the relationship between cumulative EU-years to solvents and lung function decline 171

Table 8.1 The results of my thesis by the Bradford Hill criteria to illustrate a possible causal effect relationship 192

List of Figures

Figure 2.1 COPD mortality rate ratios for 2010:1990 according to age and sex 11

Figure 2.2 Prevalence of COPD in Australia, ages 45 and over, 2014-15 12

Figure 4.1 The TAHS flow diagram and follow-ups..... 95

Figure 4.2 Work History Calendar in TAHS proband in 2002 to 2008 follow-up study 102

Figure 4.3 DAG for the association between occupational exposure and fixed airflow obstruction 109

Figure 7.1 Flow chart illustrating study design in two follow-ups..... 162

Figure 7.2 The association between cumulative years of exposure to aromatic solvents and linear predicted decline in FEV1, stratified by sex..... 172

Figure 7.3 The association between cumulative years of exposure to aromatic solvents and linear predicted decline in FVC, stratified by sex 173

Figure 7.4 The association between cumulative years of exposure to aromatic solvents and linear predicted decline in FEV1/FVC ratio, stratified by sex 174

Chapter 1 Introduction

1.1 Rationale

In my doctoral work, I have investigated the association between occupational exposure and Chronic Obstructive Pulmonary Disease (COPD), chronic bronchitis, and lung function decline in middle-aged adults. I also examined if these relationships were modified by smoking, sex, and asthma.

COPD is a collective term affecting the lungs and their structures. COPD is characterized by fixed airflow obstruction (AO) as measured by spirometry and defined by a reduction in the post-bronchodilator (BD) ratio between the forced expiratory volume in one second and forced vital capacity (FEV_1/FVC) (1). Chronic bronchitis and chronic respiratory symptoms may precede the development of fixed AO. However, they are also considered as separate conditions as not all patients with chronic bronchitis, and chronic respiratory symptoms have or will develop COPD (2, 3). Changes in lung function over time is another significant predictor of COPD and are therefore of interest for better identification of the disease (4). COPD is one of the most prevalent health care problems worldwide and constitutes one of the leading causes of chronic morbidity and mortality (5). It is now ranked as the third leading cause of death worldwide and is expected to continue to rise in coming decades (6, 7). COPD is the main contributor to the overall global disease burden (8) and is the leading disease burden in Australia (9). An estimated 460,400 Australians suffered COPD between 2014 to 2015 (10) and currently, it is the fifth leading cause of death nationwide that affects nearly 7.5% of those aged in their forties (11).

Personal tobacco smoking remains the predominant risk factor universally, but it is now well established that personal tobacco smoking is not the only risk factor for COPD (12). Occupational exposure is one of the important non-smoking related risk factors for COPD that accounts for 15-20% of COPD (13). Inhalation of small fragments of dust particles or gases in the workplace may initiate airway inflammatory processes by activating alveolar macrophages, leukocytes and by releasing reactive oxygen species in the airways, which could eventually lead to the development of lung function decline, which may in turn lead to fixed AO (14).

Studies that have investigated the role of occupational exposure in the development of COPD can be divided into those examining particular workforces or industries and those examining the general population (15). Workforce based studies often utilize direct exposure assessment to investigate the associations, whereas population-based studies usually retrospectively collect exposure information through questionnaires because direct exposure assessment in the workplace is challenging and sometimes not feasible in large-scale population-based studies (12). Studies based on the general population have examined the impact of particular occupational exposures that are derived from either self-reported or expert evaluation or by application of a Job Exposure Matrix (JEM). A JEM is a systematic computerized method for assigning exposures based on the cross-classification of job titles with a broad range of occupational exposures (16, 17). This approach has the advantage of consistently assigning the exposures, irrespective of the disease status, thus reducing the chance of differential exposure misclassification (18).

Population-based studies have suggested that occupational exposure to dust, gases or fumes increase the risk of COPD (19-22). However, these studies have had significant limitations including lack of post-BD spirometry, limited use of lifetime occupational history and cumulative exposure assessments. Furthermore, some occupational exposures with known respiratory effects (dust, gases/fumes, pesticides, and solvents) (23, 24), have not been investigated in relation to lung function decline over time in the general population. Previous studies were also limited to investigating the impact of asthma on this relationship, despite its well-recognised sequel in the causal pathway of COPD (25).

Growing evidence suggests that the prevalence of COPD is increasing in women, but the reason for this increase is not known (26, 27). Some studies have suggested that occupational exposure might be different for men and women (28) however the evidence is unclear and inconclusive.

1.1.1 Overall context of my doctoral work

For this doctoral work, I have investigated the association between occupational exposure and COPD with the aim to address some of the issues stated in the previous

paragraph. I have used data from one of the world's largest and longest running respiratory cohort studies, known as the Tasmanian Longitudinal Health Study (TAHS). This landmark study was initiated in 1968 by recruiting all seven years old school children born in Tasmania for a longitudinal study of asthma. Subsequent follow-up surveys were completed in 1974, 1979, 1991, 2002, and 2010 at the ages of 12, 18, 30, 45, and 50 years (29). From the postal survey in 2002 to 2008 follow-up, a subset of the population was selected based on a history of asthma and chronic bronchitis. This group was re-invited for laboratory investigation including lung function testing. These laboratory participants also completed lifetime work history calendars that included all jobs held during their entire working life. I performed occupational coding of 8,500 jobs in the TAHS work history calendar datasets according to the International Standard Classification of Occupations (ISCO-88) four-digit classification (30). The detailed structure, laboratory study, work history calendar, and occupational coding are described in the method section in Chapter 4. Overall, this large population-based cohort with multiple follow-ups along with spirometrically-define COPD and lifetime work histories is an ideal platform to investigate the association between occupational exposure and COPD in middle-aged adults.

1.2 Main Objectives

The overall objective of this thesis was to investigate the association between occupational exposure and COPD, using several different definitions to fully explore the relationship. The specific objectives were to:

1) Systematically examine the literature on the association between occupational exposure and risk of COPD and chronic bronchitis.
2) Investigate the association between occupational exposure and COPD defined as fixed AO, as well as chronic bronchitis and other respiratory symptoms. I also explored if these associations were modified by any factors.
3) Investigate the association between occupational exposure to solvents and metals and COPD defined by fixed AO and gas transfer factor and explore any effect modification.
4) Explore the role of occupational exposures on lung function decline and to examine any effect modification of these associations.

1.2.1 Thesis statement

This thesis is based on original research conducted throughout my PhD candidature. The longitudinal TAHS dataset has been used to examine the relationship as stated above.

1.2.2 Thesis overview

This thesis has nine chapters. The introductory chapter (**Chapter 1**) summarizes the rationale and objectives of my PhD project. **Chapter 2** summarizes the literature related to my thesis. In **Chapter 3** a published systematic review and meta-analysis titled, "Occupational exposure and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analysis" is presented. **Chapter 4**, provides a detailed description of the TAHS cohort including data cleaning, occupational coding, exposure and outcome definitions, confounding selection and statistical analysis. The findings from my original work on the TAHS are published as a paper and presented in **Chapter 5** along with an online data supplement entitled "Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age." **Chapter 6**, is a published paper titled "Occupational exposure to solvents and metals are associated with fixed airflow obstruction." **Chapter 7**, is a traditional thesis chapter titled "Occupational exposures and lung function decline". **Chapter 8** provides an overall discussion, an overview of the key findings of my PhD thesis, strengths, and limitations of my doctoral work. Finally, in **Chapter 9**, is presented with recommendations, future research directions and overall conclusions.

Chapter 2 Literature review

In this chapter, I review the burden of, definitions relating to, and risk factors for developing COPD. I then specifically discuss occupational exposures as potential risk factors for COPD; the possible biological mechanisms associated with occupational exposure; and methods of occupational exposure assessment in general population-based studies. Next, I appraise the studies that investigated occupational exposures and COPD using different definitions, respiratory symptoms, and lung function change. Finally, I explore the possibility of effect modifications of these associations by smoking, sex and asthma.

2.1 Global burden of COPD

Globally, COPD is a leading contributor to the health burden (31). Prevalence and burden of COPD is expected to continue to rise in the coming decades due to increasing global exposure to COPD risk factors, such as smoking, occupational exposures, increasing levels of air pollution, and aging of world population (32). COPD is often under diagnosed by healthcare professional because it is often unidentified until it is clinically apparent and moderately advanced, leading to an underestimation of the overall morbidity and mortality (32).

2.1.1 Global prevalence of COPD

Existing data on the prevalence of COPD shows remarkable variation due to differences in study designs, definitions of COPD, and analytic approaches. Comparison between studies investigating the prevalence of COPD is complicated by the variable use of a range of COPD definitions (e.g. physicians diagnosis, self-report or objective spirometry) and differences in the demographic characteristics of the study population (33). Different spirometric cut-off criteria and the use of pre-BD or post-BD spirometry to define COPD is also responsible for some of the variation in the estimated prevalence of COPD in the general population (33, 34). A recent meta-analysis estimated the global prevalence of COPD using stricter criteria for the included studies (35). They included studies that defined COPD using spirometry only and were published between 1990 to 2014 (35). This meta-analysis estimated that COPD prevalence increased from 10.7% in 1990 to 11.7% in 2010 (35). However, they included both pre-BD and post-BD spirometry to define COPD, which may have overestimated or underestimated the overall prevalence (35). In another meta-analysis of

COPD prevalence the pooled analysis estimated the prevalence of COPD to be between 4% and 10% (36). When they restricted the analysis to adults aged more than 40 years the prevalence of COPD was found to be between 9% and 10% (36). The variations among different studies in the prevalence estimates may be attributable to the inclusion of physician's diagnosis, self-reported and spirometry criteria to define COPD (3, 36).

The two large multi-center studies, the Burden of Obstructive Lung Disease (BOLD) study (26) and the Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO) study (37) have used gold-standard post-BD spirometry to investigate risk factors for COPD. The BOLD study was conducted in 12 sites across the world including Australia and estimated the prevalence of COPD in men to be 11.8% and in women to be 8.5% (26). However, significant heterogeneity in the prevalence of COPD was observed across all study sites in the BOLD study. The PLATINO study investigated COPD among people aged more than 40 years in five major cities in Latin America. The estimated prevalence ranged between 7.8% and 19.7% (37). As expected COPD prevalence increased with increasing age with the highest prevalence in those people aged more than 60 years. The estimates in these two studies, even with identical methodologies, show a large variability in the prevalence of COPD. This variation could be related to study locations, for example, the BOLD study was mainly conducted in the Western world, whereas the PLATINO study was entirely conducted in Latin America (5).

In summary, different study locations and study designs have been used to estimate COPD prevalence, and not surprisingly, these have reported different estimates. Prevalence of COPD also depends on demographics (age or sex) and history of individual exposure to smoking, certain environmental agents, and occupational exposures. The key to reducing the overall COPD prevalence lies in reducing exposures to those agents.

2.1.2 Global COPD mortality

Currently COPD ranks as the third leading cause of death worldwide (7, 31). Globally, nearly 3 million deaths were caused by COPD in 2015, which accounted for almost 5% of all global deaths in that year (6). In recent decades, there has been a reduction in age

and sex specific COPD mortality rates for almost all age groups, with the greatest decline among younger people, nearly in all regions (6, 38). These improvements are associated with improvement in gross national incomes (6). However, the total number of global deaths due to COPD is projected to rise by one-third over the next decade (39), due to increasing exposure to risk factors. Overall, mortality from COPD is constantly seen to be higher in older age groups, and in men compared to women (6). The death rate in women is increasing, and for middle-aged people, the mortality in women is almost equal to men (Figure 2.1) (6).

.

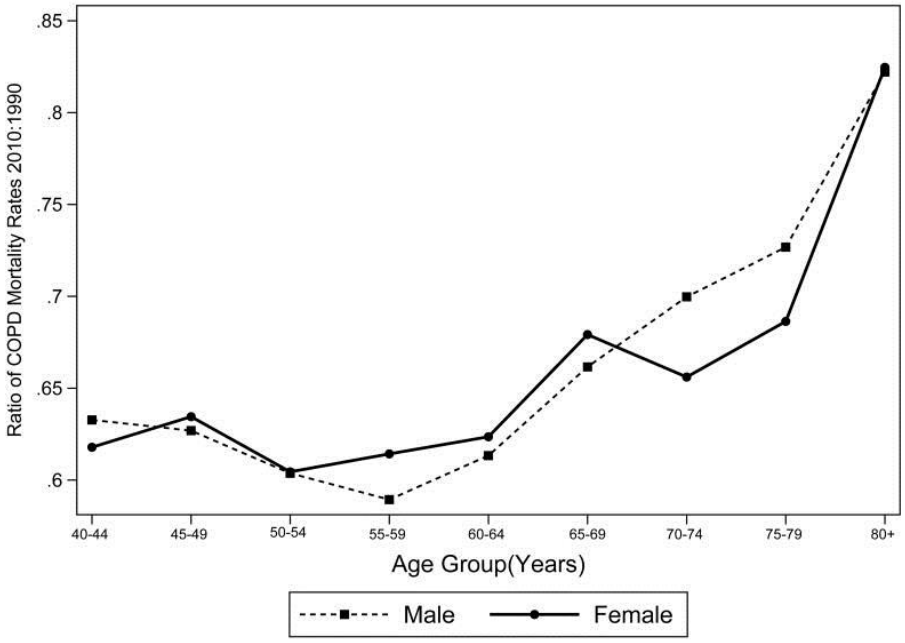


Figure 2.1 COPD mortality rate ratios for 2010:1990 according to age and sex; source: Burney et al. 2015(6)

2.1.3 Burden of COPD in Australia

In Australia COPD imposes a substantial healthcare burden and is a significant public health problem (11). The prevalence of COPD in Australia is higher among those aged older than 45 years (10). In 2014-15, the Australian National Health Survey (NHS) estimated 460,400 (5.1%) Australians aged 45 years and over had self-reported, or physicians diagnosed COPD with no significant difference between men (5.2%) and women (4.9%) (10)

(Figure 2.2). In 2011-12 the BOLD study estimated the overall prevalence of COPD in Australia to be 14.5% in those over 40 years of age and 40% in those over 75 years old (11). There were 7,025 deaths (4.6% of all deaths) attributed to COPD in 2014 making it the fifth leading cause of death in Australia. The mortality rate due to COPD in Australia is gradually declining and currently lower than that seen in the other developed countries such as the United States of America, the United Kingdom, and New Zealand but higher than France, Sweden, Japan and Finland (10).

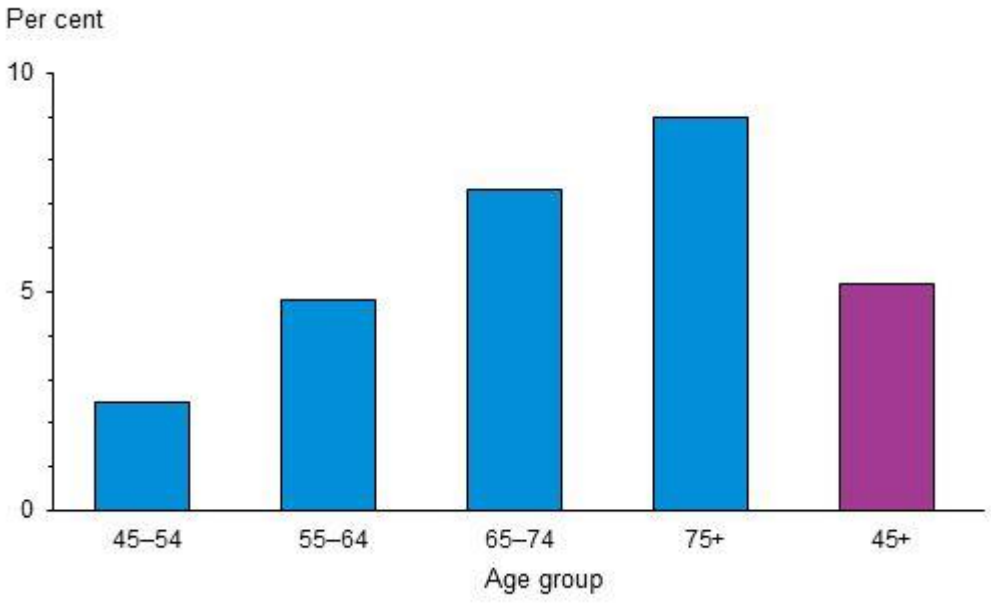


Figure 2.2 Prevalence of COPD in Australia, ages 45 and over, 2014-15 (10)

2.2 Definitions of COPD

Post-BD lung function measurement of forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) (FEV_1/FVC) ratio has been described as fundamental in defining COPD (1). This section addresses different lung function criteria that have been used to define COPD in epidemiological studies.

2.2.1 Spirometry and FEV_1 cut-off point to define COPD

Spirometry provides simple, non-invasive, and objective measurements of lung function. FEV_1 and FVC are common measures of spirometry. The risk of misdiagnosis of

COPD is less when spirometry is used because this is one of the key parameter required to confirm the COPD (40). This objective definition, based on the easily measured physiological variables, is also robust for epidemiological studies.

COPD is defined by the American Thoracic Society (ATS) and European Respiratory Society (ERS) as a common disease, characterized by persistent airflow obstruction that is not fully reversible, with respiratory symptoms and accelerated and progressive loss of lung function associated with a chronic inflammatory response in the airways due to inhaled particles or gases (1, 2). Airflow obstruction that is not fully reversible or fixed airflow obstruction (fixed AO) is defined by a reduction of the post-BD FEV_1/FVC ratio as measured by spirometry, is the hallmark feature of COPD (1, 41). The use of post-BD spirometry to define COPD is critical because it ensures a more valid diagnosis of COPD in the general population (34) by excluding those with a history of asthma (42). Post-BD spirometry is used by many international prevalence studies (1, 11, 26, 37), while few population-based prevalence studies have used pre-BD spirometry to define COPD (43, 44).

The cut-off values of FEV_1/FVC ratio that should be used to confirm an airflow obstruction has been debated (1). Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines defined COPD as post-BD fixed ratio of FEV_1/FVC less than 0.7 (2). Another definition, Lower Limit of Normal (LLN) defines COPD as an FEV_1/FVC value below the lower fifth percentile of a large healthy reference population (45). However, the GOLD cut-off may result in more frequent identification of fixed AO in elderly (46, 47) and less frequent diagnosis in younger adults aged less than 45 years (2, 46), compared with LLN cut-off values (48). The Third National Health and Nutrition Examination Survey (NHANES III) has used both GOLD and LLN definition and identified that GOLD-defined fixed ratio produced higher estimates than those of LLN estimates, particularly for older individuals (34).The Global Lung Initiative (GLI) statistical reference equation-based LLN criteria are particularly effective for epidemiological studies (48) and used in many studies to define and estimate the prevalence of COPD (47, 49).

Both of these criteria have some limitations (50). The GOLD cut-off criteria is independent of population-specific reference values and normal age-related physiological lung function decline (51, 52), which may account for more frequent diagnosis in older age. However, the GOLD-defined fixed cut-off values less than 0.7 is particularly effective and easy to use for non-epidemiologists and clinicians and therefore widely used in primary health care (34) . Several limitations occur when using LLN as the diagnostic criteria to define fixed type of AO (1, 2). LLN criteria is known to fail to identify some patients with significant pulmonary pathology and respiratory morbidity, and it is dependent on the choice of reference equations (53). In addition, LLN has not been validated using longitudinal studies (2).

Therefore, the ATS/ERS task force recently recommended using post-BD spirometry based GOLD-defined fixed ratio and GLI-based LLN criteria to define COPD and to compare the outcome, particularly when conducting large-scale population-based studies (1).

2.3 Risk factors for COPD

Although personal cigarette smoking is the predominant risk factor for fixed AO (3), it is not the only risk factor for COPD. This is evident by the fact that not all smokers develop fixed AO and not all people with fixed AO have been smokers (12). Therefore, other risk factors besides smoking are likely to be involved, and these risk factors may be broadly divided into extrinsic and intrinsic risk factors as described below (12, 54).

2.3.1 Extrinsic risk factors

2.3.1.1 Tobacco smoke

Around the world, personal tobacco smoking is the best-known risk factor for the development of fixed AO and subsequent COPD (5). Smokers have a moderately higher prevalence of respiratory symptoms and fixed AO, a greater annual lung function decline, and a higher COPD mortality rate compared to non-smokers (55). World Health Organization (WHO) estimates that 73% of COPD cases in high-income countries and 40% in low and middle-income countries are due to smoking (56). However, as this relationship was highly variable across the world and is affected by other risk factors such as occupational exposures,

air pollution, genetic effect, sex, and asthma; because not all smokers go on to develop COPD. Passive smoking exposure or environmental tobacco smoke (ETS) may also contribute to the development or COPD by increasing the inhaled particles or gases. Smoking during pregnancy may also pose a risk to fetal the lung growth and development (55).

2.3.1.2 Occupational exposures

Occupational exposures are the primary focus of my thesis, and it is a major risk factors for the development of fixed AO or COPD. I have described the effect of occupational exposure in section 2.4.

2.3.1.3 Socioeconomic status

Low socioeconomic status has been shown to be a risk factor for COPD, however, it has not yet been established which component contribute to this relationship (5). It could be due to air pollution, occupational exposures, higher rates of smoking, living or working in crowded environment, poorer nutrition, or increase risk of infection (55), with poverty regarded as a surrogate measure of these factors (5).

2.3.2 Intrinsic risk factors

2.3.2.1 Genetic factors

COPD may also develop due to the interaction between specific genes and the environment. There is evidence that genetic factors influence the development of COPD, not only in smokers but also in nonsmokers. The most common genetic factor linked to fixed AO is α1 antitrypsin deficiency, which is found in 3% of patients with AO (5). Growth factor β1, tumor necrosis factor α, Hedgehog-interacting protein (HHIP), interleukin 6 receptor (IL6R), glutathione S-transferase (GSTO2), a-Nicotinic acetylcholine receptor (CHRNA 3/5) and iron-responsive element binding protein (IREB2) may also influence the development of AO (57).

2.3.2.2 Sex

The role of sex in the development and progression of COPD is unclear and has been a topic of much research. Traditionally, COPD has been regarded as a disease of men, related

to their patterns of smoking and occupational exposures. However, growing evidence suggests that COPD is now affecting women with a severity that is equal to or even greater than that of men (58). Whether women are more susceptible to the development of COPD than men continue to be a topic of investigation, but some evidence lends support to this hypothesis (26). The effect of sex on the relationship with COPD is important since women in low and middle-income countries have low smoking prevalence compared to high-income countries but have a higher prevalence of airflow obstruction (5).

2.3.3 Other risk factors

2.3.3.1 Air pollution

Exposure to ambient air pollution has been hypothesized to be associated with increasing trend of COPD as defined by fixed AO around the world. High levels of urban traffic-related air pollution are also harmful to individuals with chronic health conditions such as heart and lung disease (55). WHO estimates that urban traffic-related air pollution maybe responsible for 1% of COPD cases in high-income and 2% in low and middle-income countries (56). A recent review from ATS also stated that air pollution is a significant predictor of lung function decline, but the evidence of a relationship between air pollution and COPD is inconclusive (12).

2.3.3.2 Asthma

Bronchial hyperresponsiveness (BHR), a hallmark of asthma has been considered as a risk factor for COPD (5). Findings from a cross-sectional study have shown an overlap between COPD and asthma of up to 30% (59). It has also been reported (in a longitudinal study) that people with asthma lose lung function more rapidly compared to people without asthma (60). Another longitudinal study found that 20% of people with asthma and BHR may develop irreversible fixed AO and lung function decline compared to non-asthmatics (61). BHR may also exist without asthma and has been found to be associated with COPD (62) and an excess decline in lung function (63).

2.4 Occupational exposures as a risk factor for COPD

Occupational exposures to dust, chemicals, vapors, gases, and fumes also significantly contribute to the development of fixed AO or COPD. It has been estimated that 19% of COPD cases in the United States of America (USA) were attributed to occupational exposures, with 31% being in people who have never-smoked. These estimates are consistent with ATS that concluded that workplace exposure contributed to 15% to 20% of all cases of airflow obstruction (13). Occupational exposure in less regulated areas of the world is likely to be higher than that reported in studies from developed countries with well-developed occupational health and safety surveillance and disease prevention systems. To date, however, work done to investigate specific workplace exposure for the development of COPD has been, limited and inconsistent.

2.4.1 Biological impact of occupational exposure on the respiratory tract

Exposure to occupational agents leads to inhalation of the gases or particles into the respiratory tract through the nose or mouth, primarily causing airway blockage. Upon inhalation, particles are first deposited and remain in the respiratory tract according to their size, and shape (64). The deposition pattern of particles differs, depending on the route of inhalation and the size of particles. For example, fine particles, such as dust generated by fine sanding, may travel beyond the nasal cavities and into the lungs. Deposition of large numbers of foreign particles in the alveoli leads to macrophage overloading and impaired phagocytosis, and results in interstitial accumulation of particles that leads to inflammation (64). The inflammatory mediators such as cytokines that are released from the overloaded macrophages primarily initiate the inflammation. During the inflammatory process, leucocytes create a communication between the infiltrating cells and the affected tissue through cytokines. Cytokines binds to the membrane receptors causing excess mucus secretion and smooth muscle contraction in the airways, which leads to breathlessness, cough, and wheeze.

Inhalation of vapors, dust, chemicals, gases or fumes can adversely affect any part of the respiratory tract. The part of the respiratory tract affected depends on the immune status of the individual and the nature and properties of the inhaled particles or gases. Acute

inhalation of an occupational exposure can cause injury to the respiratory tract which may result in breathlessness, cough, phlegm production and chest tightness. This usually requires immediate medical treatment. The extent of damage to the respiratory tract depends on the cumulative dose of exposure and may lead to prolonged symptoms. Long latency periods may exist between the acute inhalation exposure and subsequent development of the chronic airway disease. This latency period may be from years to decades and may cause long-term diseases such as fixed AO that leads to COPD (14).

2.4.2 Population-based versus workplace-based studies

The health effect of occupational exposures can be explored either in workplace settings or in the general population (65). Studies in workplace settings are usually more specific to the hazards present in the workplace and the degree of risk at various exposure levels (66). They also offer an opportunity to obtain high-quality exposure information for the period of the study or across the working life of the participants. However, occupational cross-sectional studies are prone to survivor bias or the healthy worker effect because workers who have left their jobs because of previous respiratory problems may not be included in the study. In occupational cohort studies, there may be loss to follow-up, thereby once again underestimating the true impact of the exposure (12). They are also designed to identify specific diseases among the exposed workers, for which, the results may not be generalizable to the broader population. Despite these limitations, over the past two decades several workplace-based studies among cement workers (67), construction workers (68), farmers (69), and textile workers (70) have shown a clear association between occupational exposure and COPD.

Although workplace based studies have provided evidence that occupational exposure is associated with AO, it has also been suggested that this link could be established using population-based studies (12). Population-based studies involves both cross-sectional and longitudinal follow-up of members of the general population for a certain period to observe exposure-outcome relationships (71). In population-based studies, the source population is the general population, and they may or may not be exposed to certain occupational agents whose level of intensity may have changed over time (16). The external

validity of the population based study design is considered enhanced because of its source population and the applicability of its results to the general population (71). A major advantage of population-based studies is that the problem of healthy worker effect can be avoided to a large extent (12, 13, 65). Furthermore, although the population-based study design is not typically intended to examine the relationship between occupational exposure and airflow obstruction; they nonetheless can provide the strongest evidence for an association (12).

2.4.3 Assessment of occupational exposure in the general population

In general population-based studies, people tend to work in a wide range of occupations during their working lives. Therefore, assessment of occupational exposure is often challenging (65). Great reliance is placed on participants to accurately recall their past work histories and duration of employment. Participants may have been previously exposed to several chemicals, biological and physical agents with the level of intensity of exposure changing over time. Quantitative measurements of individuals' exposure are rarely available so it is not possible and often does not allow for estimation exposure retrospectively. Therefore, studies in general populations need to utilize retrospectively collected lifelong historical occupational exposures data. This is because there may be a long latency period between occupational exposure and COPD occurrence.

Assessment of retrospective exposure in various occupations is often complicated due to task changes and the mix of work tasks within the same jobs. Workplace conditions can also change in response to new technologies, new regulations, product demand fluctuations, or product formulation variations. Employees may also perform multiple tasks at the same time and be rotated between jobs as production demand changes. All these workplace changes make the identification of occupational exposures in general population-based studies complex.

Several methods have been used to assess occupational exposures in population-based studies. Two common approaches used to collect the information from questionnaires are, when job title is used as a proxy for exposure assessment, and when information on

occupational exposures are gathered from self-reported occupational histories. These two methods can be integrated by expert evaluation, or by the occupational hygienist, or by the application of Job Exposure Matrices (JEMs) to the self-reported work histories (72).

The basic principles of each of these methods along with their advantages and disadvantages are discussed next.

2.4.3.1 Job title

The complete lifetime work history calendar is the basic information that is usually collected in the questionnaire. It contains information on detailed job histories including a list of all jobs held throughout the person's working life, nature of employment, name, and description of the industry, starting and ending date or year. In some cases, to minimize both time and cost, information on only the last or the most recent job held or the longest duration job is collected. The job title method is relatively inexpensive, is an easy way to collect the information, and facilitates large-scale analyses (16). It is also useful for epidemiological surveillance of occupational risks. It has frequently been used as an exploratory tools for identifying jobs at high risk of morbidity and mortality (73).

The job title based occupational information does not guarantee data quality. Even, if the job is well described and the participants' have provided detailed information, the job and activity sector may affect the exposure assessment. Therefore, it is important to collect the information related to subjects' job history and task activity (if possible) to assign the most appropriate job coding. However, additional information on job activity may complicate the questionnaire and may be not feasible due to time constraints. Participants may have moved between many activities within a given job and, therefore, capturing this information in a useful and reliable way may be difficult and may result in misclassification. In addition, the coding procedure requires special training, knowledge of the job or activities in the sector, and the ability to use several different coding guidelines. Hence it is important to check the quality of coding to ensure proper job classification and to reduce bias (73).

2.4.3.2 Self-reported exposure

The self-reported exposure assessment method involves collecting information on occupational exposures directly from participants using a questionnaire. This is often in the form of multiple-choice questions regarding substances used by employees in their workplace. However, in general, the ability to report individual chemical substances requires the subject to recall whether they were exposed, and/or actually know that they were exposed. Some occupations such as gardeners or farmers who use pesticides may be exceptions because they need to keep the purchase records and use personal protective equipment (PPE) (16). One limitation of this method is reporting bias that may result in differential misclassification of self-reported exposures (74). To reduce this misclassification bias, self-reports obtained from questionnaires should not be used on their own to assess occupational exposure, but should be integrated with other workplace information, such as tasks undertaken and other detailed features of their occupational history. However, a major disadvantage of job-specific questionnaires or interviews compared to the simple self-reported questionnaire is their high cost; they also involve labor-intensive processes (72).

In order to collect a complete occupational history with a self-reported questionnaire, a detailed job-specific questionnaire along with a checklist of tasks performed can be developed (72). This type of questionnaire allows the filtering of the most appropriate questions for the participants. In addition, self-reported exposure information can be collected via face-to-face interview or telephone questionnaire. A face-to-face interview allows collection of detailed data with completeness. This method generally results in higher response rates and the lower incidence of missing data. In the case of telephone interviews, trained interviewers can collect information that is more complex, but the response rate is often lower compared to face-to-face interviews.

2.4.3.3 Expert assessment

The expert evaluation by either an industrial hygienist, a panel of industrial hygienists or a toxicologist is considered to be the gold standard method. It has been shown to provide the most accurate means of measuring occupational exposure in population-based case-control studies (16, 75). It is a lengthy procedure that requires a structured questionnaire

along with knowledge and expertise of one or more experts. After each job history has been obtained via interview using a structured questionnaire, the experts first review the data to assess whether the individual has been exposed to each occupational agent of interest, then rate the intensity of exposure on a scaling system to classify the subjects (16). This method is usually applied at the individual level and therefore considers case-by-case evaluation that also takes into account the subjects' tasks and exposure conditions at the workplaces.

There are several concerns when using expert opinions to assess occupational exposures (16). It depends on the quality of the questionnaire and the training of interviewers. Hence, questionnaire responses can be affected by differential and non-differential reporting bias. Therefore, overall validity partly depends on the validity of the subject reporting and partly on the experts' judgments. Other concerns are the high cost of using experts to assess occupational exposure; it is a time-consuming procedure; and therefore may not be practical in large-scale studies (16). I If the assessment is undertaken over a number of years then the knowledge and expertise of the expert may change during the evaluation process, therefore the classification of subjects at the beginning and at the end of the study may not be the same. Expert evaluation also requires experts to be have a broad knowledge of both small and large enterprises (72). The validity of the expert assessment method also depends on the quality of the available data which may vary in quality (76). Finally, qualified experts are scarce and have other professional commitments.

2.4.3.4 Job Exposure Matrices (JEMs)

To improve exposure assessment by the use of job title only, in the late 1970s, occupational epidemiology started to develop the first computerized Job Exposure Matrices (JEMs) to assess occupational carcinogen exposures (17, 18). The JEM is a systematic tool for assigning exposure based on the cross-classification of a list of job titles with a list of agents (16, 17). The JEM can be seen as a cross table, which lists a broad range of exposure agents on one axis, called the "exposure axis"; and a range of occupational classifications based on job title on the other axis, called the "job axis." The job axis includes job titles of a general classification of employment, and the exposure axis can vary from categorical grouping of exposures (for example, dust exposure–yes/no) to detailed individual exposures

(18). Exposure can be automatically linked to subjects, based on the job title (77). The assessment of exposures in JEMs can be either dichotomous (for example, exposed/non-exposed) or ordinal (for example, no, low or high) exposure variables (16). Recent developments have also introduced semi-quantitative indexes, such as calendar time and gender, that often allow a third axis to account for change in exposure over time and increase their validity (18).

Different types of JEMs were developed according to their context of use, such as general population-based JEMs (GPJEMs), agent-specific or disease-specific JEMs and industry-specific JEMs (ISJEMs) (18). Population-based JEMs cover all jobs or occupations of a general (nationwide) classification, whereas agent-specific JEMs may have a matrix restricted to job titles occurring within the industry, or even within one facility (78). However, regardless of the types of JEMs, it is necessary to choose a standard job classification system. The choice of job classification system could be either national job classification or international job classification. The use of a national classification can be limiting. , This matrix can be difficult for researchers in other countries to use, as it is time consuming and expensive to recode or translate the job titles. Additionally, it could lead to loss of information if the job title cannot be translated, or it can be affected by misclassification due to differences between coders and differences in translation of codes (65). Therefore, it necessary that well-trained coders with basic knowledge of jobs performed in the different industries, undertake the job coding. A consensus exists for the use of international coding systems for industries (International Standard Industrial Classification, ISIC) (79) and the general population (International Standard Classification of Occupations, ISCO) (30). Other than these classifications, some countries have their own job classification systems that are more or less similar to the international classifications. One example is the Finnish Job Exposure Matrix (FINJEM), designed by the Finnish Institute of Occupational Health (FIOH) in 1990, based on the Finnish occupational coding system (74). FINJEM is also a general population-based JEM that provides quantitative information on exposure to different agents (80). Recently, researchers have been trying to develop a new JEM based on national occupational coding classifications (80). Australia has been in the process of

formulating a new JEM, AusJEM, since 2010 based on Australian Standardized Coding of Occupations (ASCO) (81).

JEMs have been used for many years in occupational epidemiology and have been proven useful for management, surveillance, and intervention purposes in the occupational health sector (82). They are an efficient, cost-effective, and reliable way to evaluate the link between occupational exposure and disease in population-based studies allowing for more accurate analysis of exposure-outcome relationship rather than looking at the job title alone (18). They also overcome the shortage of qualified experts in a wide range of exposures. Furthermore, they can be used where traditional exposure assessment methods may not be applicable, such as in large-scale studies. A further advantage of JEMs is that they consistently assign exposures, irrespective of the disease status of the subject, ultimately eliminating differential information bias, since exposure allocation is blinded to case status (18).

Unfortunately, a major limitation of JEMs is that they cannot take into account the variability of exposure within the same job categories or same occupational classifications. JEMs may misclassify participants into the exposed group when they are not truly exposed because they are only using job title to assign exposure. However, this misclassification is likely to be non-differential on a participant's disease status (18). To minimize misclassification, the best method to assess exposure is to collect lifetime work histories (78). A recent review of the methodology of JEMs demonstrated the need for further research using JEMs along with lifetime work histories to reduce exposure misclassification (16). JEMs also allow the study of occupational exposures in population-based longitudinal studies that is less affected by the healthy worker effect or the survivor effect (16).

Overall, JEMs are useful tools to describe exposures in general population studies as they are assigned exposures based on job title and self-reported lifetime work history calendar. They are limited by possible misclassification of exposure due to variation in exposure levels with different tasks within the same job title or within different companies

or industries. The development of matrices based on job tasks rather than job titles would advance the area, however, they are not currently available.

2.4.3.4.1 JEMs applied in the general population

Based on the early JEMs developed for carcinogen exposures in the early 1980s, researchers from the Netherlands, Professor Hans Kromhout and Associate Professor Roel Vermeulen, developed a modified version of a population-specific JEM for the ECRHS-I study in 1998. This was based on the Population Census and Surveys (OPCS) classification of occupations (83). This JEM was named the Ad hoc JEM, and was used to examine the association between occupational exposures and airflow obstruction. Subsequently, the Spanish site of the ECRHS-II study, changed and coded JEM according to International Standard Classification of Occupation (ISCO-88) (84). This JEM was later re-named the ALOHA JEM *(A Lot of Occupational Hygiene Assumptions).* ALOHA JEM was first applied in an Australian study that investigated occupational exposures and airflow obstruction (19). In the first version of the ALOHA JEM exposures were classified into biological dust, mineral dust, gases/fumes and a combined measure of vapor, gases. dust, and fumes (VGDF). The later version of the ALOHA JEM includes exposures to pesticides, organic solvents, and metals and has been renamed the ALOHA plus JEM (85). Both of these JEMs were designed according to the ISCO-88 classification and used work history calendars to assign exposures. Based on job title and ISCO-88 classifications, the ALOHA plus JEM assigned exposures into high or low exposures to biological dust, mineral dust, and gases/fumes, VGDF, pesticides, herbicides, insecticides, aromatic solvents, chlorinated solvents, other solvents, and metals (85).

2.5 Lifetime occupational exposure versus current job exposure

Precise and valid retrospective work history collection is the primary challenge in occupational epidemiological studies. A variety of methodological techniques have been used in occupational studies to collect accurate retrospective work histories (86). Collection of lifetime work history calendars are critical to complete retrospective exposure assessment (87). Lifetime work history calendars provide an ideal opportunity to capture the length of jobs and changes of exposure through the jobs over time in the working population.

Lifetime work history calendars collect information about previous work histories using a general questionnaire on the duration of employment, and therefore, it is possible to calculate cumulative duration of exposure from lifetime work history calendars (87). Cumulative exposure is a multiplicative product of exposure level and duration of employment that indicates total amount of exposure that workers have been exposed over time. Assessment of cumulative exposure also indicates any dose-response relationship between exposure level and outcome of interest. Using lifetime work history calendars also helps to minimize survivor bias or healthy worker effect. Individuals most affected by respiratory symptoms at the time of their working life may change jobs or alter their working environment to reduce the level of exposure. Lifetime work history calendars allows capturing all past exposures even in those who have moved from a highly exposed job into low exposed or not exposed job.

Several studies have assessed the methodological approaches of lifetime work history calendars. Engle et al. used a calendar-based questionnaire and compared the traditional occupational questionnaire among the farmworkers to capture the length of jobs and concluded that the calendar-based technique is more effective for collecting a complete picture of a person's work history rather than the traditional questionnaire-based method (88). Zahm et al. also used a lifetime work history technique using a calendar-based method and demonstrated that this technique was effective for collecting complex work histories and related risk factor data among farmworkers (89). Hoppin et al. also described the appropriateness of lifetime work history calendars to recall and collect previous work histories by the worker (86). This study also concluded that use of lifetime work history calendars was useful for understanding the nature of the exposure-outcome relationship and effective for collecting information on time-varying exposures, duration, and intensity of exposures to reduced potential measurement error.

Numerous studies have used current or most recent job exposure instead of lifetime work history calendars (20, 83-85, 90). Current or most recent job does not adequately account for previous exposures, and the analyses can be erroneously based only on most

recent or current job exposure. Using a current job may increase the chance of missing an important previous exposure. In current job analysis, it is also not possible to identify healthy worker bias that may also affect the association. Therefore, it is likely that current job exposure may underestimate or overestimate the true impact of occupational exposure on lung health (91, 92). In occupational epidemiological studies of the fixed nature of AO, it is essential to focus on previous exposure as well as cumulative exposure due to the long latency period that may exist between occupational exposure and the development of COPD.

In the next section, I will explain the respiratory health effect of occupational exposures with the particular focus on respiratory symptoms, chronic bronchitis, and COPD as defined by fixed AO. I will also summarize the epidemiological literature related to the effect of occupational exposures on lung function decline.

2.6 The association between occupational exposures, and respiratory symptoms, chronic bronchitis, and COPD

In this thesis, I have focused on the occupational exposure defined in the ALOHA plus JEM that includes exposures to biological dust, mineral dust, gases/fumes, combined exposures to VGDF, all pesticides, herbicides, insecticides, aromatic solvents, chlorinated solvents, other solvents, and metals. In this section, I will discuss the literature that has specifically evaluated the effect of each of these exposures and their relationship with respiratory symptoms, chronic bronchitis, COPD defined by fixed AO, and lung function decline over time.

2.6.1 Biological dust exposure

2.6.1.1 General overview

Biological dust usually includes substances of microbial, plant, or animal origins such as pathogenic or non-pathogenic bacteria, viruses, fungi, toxins, spores, allergens, peptidoglycans, glucans, pollens, and plant fibers. In general, biological dust is a complex mixture of one or more of these substances (93). The interest in biological dust exposure has increased over the last few decades, because it has been recognized that exposure to biological dust in the workplace is associated with a wide range of adverse health effects, including respiratory diseases. Respiratory symptoms due to occupational exposure to biological dust can range from acute inflammation by toxins to chronic severe inflammatory response within the lungs (93). Respiratory symptoms and airflow obstruction are t common health effects that are associated with biological dust exposure.

There are a huge range of occupations that are exposed to biological dust. These occupations include, but are not limited to, workers in animal husbandry, plant agriculture, forestry, health care, textiles, paper production, fishery and aquacultures, food production and processing (94, 95). Some common occupations related to biological dust exposure are listed in Table 2.1 (below).

Table 2.1 Industries with biological dust inhalation hazards

Occupations/Industry	Types of biological dust	Tasks associated with exposure
Agriculture	Allergenic and toxinogenic bacteria, fungi, mites etc	Breeding animals, cultivating plants, gardeners
Animal husbandry	Zoonotic bacteria, viruses, fungi, parasitic worms etc	Work activities where there is contact with animals or products of animal origin (or both)
Biotechnology	Endotoxin of Gram-negative bacteria, zoonotic viruses and bacteria	Production of single cell protein, snow inducer, detergent factories, cooks
Clinical, veterinary and diagnostic laboratories	Zoonotic bacteria, viruses, fungi, parasites	Veterinarians, workers in the zoos, museums, taxidermists
Health care	Infectious agents of human origin, hepatitis B virus, adenovirus, mumps virus, rubella virus etc	Isolation and post mortem units, funeral and cremation undertakings.
Pharmacists	Pharmaceutical powders, allergenic drugs of microbial origin	Production of pharmaceutical products
Sewage, compost solid, agriculture waste workers	Enteric bacteria, viruses, hepatitis A virus, fungi	Handling, moving, transporting of waste

2.6.1.2 Association between biological dust exposure and respiratory symptoms, and chronic bronchitis

Several industry-based studies have demonstrated that biological dust exposure resulting from agriculture work is associated with chronic bronchitis, and respiratory symptoms. Dalphin et al. studied the effect of biological dust exposure in France and found increased prevalence of chronic bronchitis (96). Eduard et al. compared the likelihood of chronic bronchitis and COPD among crop and livestock farmers (69). This study also demonstrated that livestock farmers were more likely to develop chronic bronchitis than crop farmers due to biological dust exposure, although the effects of specific biological substances could not be assessed (69). Monso et al. conducted a study among non-smoking European animal farmers working inside confined buildings and suggested that there was a 17% higher risk of developing reversible AO (97). Furthermore, they also observed a dose-response relationship with a greater risk of COPD in those with higher biological dust, and endotoxin exposure (97).

Most studies that evaluated biological dust exposure were conducted in a specific workplace environment. However, several population-based studies have also explored the relationship between biological dust exposure and respiratory symptoms and chronic bronchitis (Table 2.2). Of the 13 studies that investigated the association between biological dust exposure and respiratory symptoms, two studies reported a significant association between biological dust exposure and symptoms of cough, phlegm, and dyspnea (98, 99). Nine studies investigated the association between any biological dust exposure and chronic bronchitis; of them, three studies reported significant associations (100-102). The other six studies, however, found no association between biological dust exposures with chronic bronchitis (19, 23, 103-106). The two studies that found the association with chronic bronchitis used a questionnaire-based self-reported method to assess biological dust exposure (100, 101), which may have introduced differential misclassification bias. In addition, both studies assessed dust exposure in cotton, wood, metal, minerals, asbestos, and grain dust in agricultural workers, which further indicates that a large number of participants from specific occupational groups influenced the association. One study from the Netherlands found a significant association between biological dust exposure and chronic bronchitis using a JEM based exposure assessment (102). There were inconsistencies in the definition of chronic bronchitis. Only three studies used a combination of cough and phlegm that was present for more than 3 months for the last 2 years; whereas the other studies used the last 1-year to define chronic bronchitis, which may have underestimated the overall effect. Three studies investigated cumulative biological dust exposure, but none found a significant association with chronic bronchitis (19, 103, 105).

In summary, the evidence for an association between biological dust and chronic bronchitis and respiratory symptoms are inconsistent. However, inconsistent findings were mainly due to differences in the exposure assessment method and lack of standardized definition of symptoms or diagnosis. Detailed information on the studies that assessed this relationship are presented in Table 2.2 (below).

Table 2.2: Population-based studies investigating the association between biological dust exposure and respiratory symptoms and chronic bronchitis

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of job	Definitions used	Any exposure OR(95%CI)	Cumulative exposure (years) OR(95%CI)
Cross-sectional studies							
Hansell et al.(2014) (103)	New Zealand	1,017	ALOHA JEM	Lifetime WHC	CB:cough,sputum≥ 3months/yr≥1 yr	H= 1.08(0.51-2.28) L= 1.61(0.92-2.83)	1.34(0.65-2.76)
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	CMH:sputum≥3months/yr≥1yr	H= 0.86(0.48-1.55) L= 1.19(0.91-1.56)	N/A
Lam et al. (2012)(98)	China	8,216	SR		Cough	H= 1.76(1.23-2.53) L= 0.77(0.48-1.23)	N/A
					Dyspnea	H= 1.4(1.19-1.64) L= 1.13(0.96-1.33)	
Skorge et al. (2009) (107)	Norway	2,312	ALOHA JEM	11 years job	Cough	H=2.48(1.2-5.2)	N/A
					Dyspnea	H=1.44(0.7-3.0)	
Krstev et al. (2008) (105)	China	14,500	SR	Lifetime WHC	CB: doctor diagnose	1.09(1.00-1.18)	1.06(0.96-.17)
LeVan et al. (2006) (100)	Singapore	52,325	SR	Current and previous job	CB:Cough,phlegm≥3months/yr ≥2yrs	1.26 (1.01-1.57)	N/A
					CMH: cough/phlegm	1.08 (0.95-1.22)	
Matheson et al. (2005) (19)	Australia	1,213	ALOHA JEM	Lifetime WHC	CB: phlegm≥3months/yr≥2 yrs,	CB= 1.74(0.97-3.11)	CB in men 1.38(0.26-7.30)
					Cough	Cough= 1.25(0.80-1.94)	CB in women 4.65(0.83-26.0)
					Dyspnea	Dyspnea= 1.35(1.01-1.79)	
de Meer et al. (2004)(106)	The Netherlands	1,906	JEM	Current job	CB: cough and phlegm≥3months/yr≥1 yr	CB= 0.89(0.56-1.42)	N/A
					Wheeze	Wheeze= 1.06(0.79-1.42)	
Suadicani et al. (2001) (101)	Denmark	3,331	SR	>5 years job	CB: cough and phlegm≥3months/yr≥2 yrs	1.5(1.1-2.1)	N/A
Sunyer et al.(1998) (83)	Spain	1,735	ALOHA JEM	Current job	Cough	H=1.9(0.9-3.7); L=1.5(1.0-2.3)	N/A
					Phlegm	H=1.6(0.8-3.3); L=1.2(0.8-1.7)	
Heederik et al. (1989) (102)	The Netherlands	828	JEM	Longest job	CB: doctors' diagnosis, Dyspnea	OR=0.89 for dyspnea and 2.46 for CB	N/A
Korn et al. (1987) (99)	USA	8,515	SR	Lifetime WHC	Cough	Cough= 1.32(1.14-1.52)	N/A
					Dyspnea	Dyspnea= 1.6(1.35-1.91)	
Cohort study							
Heederik et al. (1990) (23)	The Netherlands	804	JEM	Longest job	CNSLD: doctors' diagnosis	1.16(0.74-2.86)	N/A

Definition of abbreviations: CB= Chronic Bronchitis; CNSLD= Chronic Nonspecific Lung Disease; CMH= Chronic Mucus Hypersecretion; WHC= Work History Calendar; USA=United States of America; N/A= Not Available; H=High Exposure; L=Low Exposure; OR=Odds Ratio; CI= Confidence Interval; SR=Self-Reported Exposure

2.6.1.3 Association between biological dust exposure and COPD

Population-based studies suggest an association between biological dust exposure and COPD defined by fixed AO (summarized in Table 2.3). Of the 12 studies presented in Table 2.3, 10 studies investigated prevalence (19, 83, 85, 98, 99, 103, 104, 108-110), while two studies investigated incidence (20, 84). Most studies used the ALOHA JEM to assess the exposure, and of those, only two studies used lifetime occupational history (19, 103), while others used most recent or current job. Only two studies used post-BD spirometry to define COPD (103, 110). In terms of spirometric cut-off criteria, five studies used $FEV_1/FVC<0.7$ (19, 83-85, 104) and five studies used $FEV_1/FVC<LLN$ (98, 103, 108-110) and one cohort study used both to define COPD or fixed AO (20).

Two recent studies from a Danish population-based cohort, conducted two separate cross-sectional analyses (108, 109). One including the whole cohort (109), and the other focussed on never-smokers only (108). Both analyses produced very similar results and found significant associations between any exposure to organic dust with airflow obstruction. However, both analyses used a self-administered questionnaire, where the participants were asked about their exposure to biological and inorganic dust during the previous 5-years. Four cross-sectional (83, 85, 103, 104) and two cohort studies (20, 84) used the ALOHA JEM to assess occupational exposure, but these studies did not find significant associations between biological dust exposure and airflow obstruction. Only one study from New Zealand (103) used post-BD spirometry to define COPD, whereas all other studies used pre-BD spirometry, that does not allow for the assessment of fixed AO or COPD. One Australian study that assessed exposure using the ALOHA JEM found that any biological dust exposure was associated with COPD, where COPD was defined using a combination of spirometry, carbon monoxide lung transfer factor (T_{LCO}), and respiratory symptoms of cough, sputum and dyspnea (19). This study, however, did not find a significant association with airflow obstruction when the definition of pre-BD $FEV_1/FVC<0.7$ was used. This study also investigated association between cumulative biological dust exposure and COPD, and found that cumulative exposure to biological dust was associated with COPD in women but not in men. One large European cohort study also examined cumulative exposure and found an association between biological dust exposure and AO as defined by pre-BD spirometry (20).

In summary, the evidence for an association between biological dust and COPD in the general population remains unclear. A number of studies used pre-BD to assess this relationship, which does not allow for the assessment of fixed AO or COPD. The null findings reported in some studies may be due to the use of pre-BD spirometry, use of current job rather than lifetime occupational history, and lack of statistical adjustment for asthma These factors may have underestimated the true impact of biological dust on COPD in general population studies. Further information regarding the association between biological dust and COPD is presented in Table 2.3 (below) and Chapter 3.

Table 2.3: Population-based studies investigating the association between biological dust exposure and COPD

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of job	Definitions used	BD	Any exposure OR(95%CI)	Cumulative exposure (yrs) OR(95%CI)
Cross-sectional studies								
Tagiyeva et al. (2016) (110)	UK	328	JEM	Lifetime WHC	FEV_1/FVC< LLN	Post	1.07(0.58-1.99)	No association
Würtz et al. (2015) (108)	Denmark	1,575 (Never smokers only)	SR	NM	FEV_1/FVC< LLN	Pre	2.94(1.05-8.22)	N/A
Würtz et al. (2014) (109)	Denmark	4,717 (Whole sample)	SR	NM	FEV_1/FVC< LLN	Pre	1.56(1.09–2.24)	N/A
Hansell et al.(2014) (103)	New Zealand	1,017	ALOHA JEM	Lifetime WHC	FEV_1/FVC< LLN	Post	H= 0.96(0.43-2.13) L= 0.95(0.50-1.83)	0.93(0.43-2.04)
de Jong et al. (2014)(85)	The Netherlands	11,851	ALOHA plus JEM	Current job	FEV_1/FVC< 0.7	Pre	H= 1.04(0.92-1.18) L= 0.91(0.66-1.25)	N/A
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	FEV_1/FVC< 0.7	Pre	H= 0.86(0.33-2.25) L=1.14(0.74-1.74)	N/A
Lam et al. (2012)(98)	China	8,216	SR	Longest job	FEV_1/FVC< LLN	NM	H=1.36(0.99-1.88) L= 0.92(0.64-1.32)	N/A
Matheson et al. (2005)(19)	Australia	1,213	ALOHA JEM	Lifetime WHC	FEV_1/FVC< 0.7	Pre-men	1.49(0.63-3.51)	0.81(0.22-2.94)
						women	7.43(2.07-26.7)	6.9(1.75-27.2)
Sunyer et al.(1998)(83)	Spain	1,735	ALOHA JEM	Current job	FEV_1/FVC<0.7	Pre	H=1.7(0.3-8.2) L= 1.6(0.6-3.9)	N/A
Korn et al. (1987)(99)	USA	8,515	SR	Lifetime WHC	FEV_1/FVC<0.6	Pre	1.53(1.17-2.00)	N/A
Cohort studies								
Mehta et al. (2012) (20)	Switzerland	4,267	ALOHA JEM	Current job	FEV_1/FVC<0.7	Pre	H= 0.93(0.63-1.44) L= 1.00(0.81-1.24)	1.15(1.04-.26)
					FEV_1/FVC< LLN		H=0.94(0.46-1.95) L=1.09(0.80-1.50)	1.11(0.99-1.24)
Sunyer et al. (2005)(84)	Spain	6,481	ALOHA JEM	Current job	FEV_1/FVC<0.7	Pre-men	H= 1.34(0.17-10.3) L= 0.39(0.05-2.99)	N/A
						women	H=2.91(0.37-22.86) L=0.55(0.16-1.91)	

Definition of abbreviations: BD= Bronchodilator; CI= Confidence Interval; H=High Exposure; L=Low Exposure; LLN= Lower Limit of Normal; NM=Not Mentioned; N/A= Not Available; OR=Odds Ratio; SR = Self-Reported Exposure; USA=United States of America; UK= United Kingdom;; WHC= Work History Calendar

2.6.2 Mineral dust exposure

2.6.2.1 General overview

Mineral dust is an airborne aerosol emitted from the suspension of minerals from the tiny soil particles that are not always visible and contains various oxides and carbonates (111). Crystalline silica, mainly in the form of quartz, is one of the common natural mineral dusts that forms the major component of hard rocks (for example, granite), soft rock (for example, sand, gravel), and soil (111). Therefore, stonework and grinding related industries involve workers potentially exposed to different types of mineral dusts which include gold mining, concrete production, construction work, tunnel work, cement production industry, brick manufacturing industry, quarry workers, underground mineworkers, ceramic industry, and iron, and steel manufacturing industry (112, 113). Inhalation of mineral dust, such as coal, silica and other finely powdered materials may initiate fibrotic changes in the lung parenchyma followed by gradual damage to respiratory health (114). Larger dust particles that are visible to the naked eye usually deposit in the nose and respiratory tract but the tiny particles <10 μm in diameter (respirable particles) can easily be inhaled deep into the lungs (112).

Long-term exposure to inhalable mineral dust can lead to serious respiratory issues including silicosis, coal workers' pneumoconiosis, COPD, and cancer (112). Mining, maintenance and processing activities, were the first occupations that were associated with severe parenchymal lung abnormalities or pneumoconiosis and significant reduction of lung function (112). Studies to date have shown that mineral dust exposure is an independent predictor for developing pneumoconiosis, chronic bronchitis, COPD, fibrosis, and emphysema (115-117). Sometimes, the feature is correlated with emphysema or parenchymal destruction independent of cigarette smoking among coal miners and hard-rock miners (116-118). Besides coal mining, several other occupational mining works such as gold, copper, iron, talc, potash, kaolin have also been found to be associated with chronic bronchitis (119). Studies on rescue workers, residents, cleaners, and volunteers exposed to multiple specks of dust following exposure during the 2001 World Trade Center incident suggest an increased incidence of bronchial hyperresponsiveness, cough, and phlegm (120). Another study on

residents exposed to World Trade Centre dust demonstrated emphysematous and small airway changes and macrophages containing silica, aluminum, titanium dioxide, talc, and metals (121). Findings from this study also suggested that workers exposed to mineral or inorganic dust particles following the World Trade Centre exposure may have a higher risk of developing fixed airflow obstruction. Some common respiratory health effects associated with mineral dust exposure are listed below in Table 2.4.

Table 2.4: Industries with mineral dust exposure

Occupations/Industry	Types of mineral dust	Respiratory health effect
Construction workers	Lead, manganese, cadmium, silica, and zinc	Systematic toxic effect on absorption, silicosis
Timber/sawmill	Woods, organic and inorganic chemicals	Allergic reactions, respiratory symptoms
Concrete production	Asbestos, crystalline silica, chromates	Lung fibrosis and cancer
Cement production	Acid, alkali	Mucous membrane irritation
Mining	Coal dust	Respiratory diseases including coal workers' pneumoconiosis, fixed airflow obstruction, bronchitis, emphysema and silicosis

2.6.2.2 Association between mineral dust exposure and respiratory symptoms, and chronic bronchitis

Few population-based studies have assessed the association between occupational exposure to mineral dust and respiratory symptoms and chronic bronchitis (summarized in Table 2.5). Of the nine studies presented in Table 2.5, eight studies examined mineral dust using the JEM based exposure assessment, and of those, only two studies (19, 103) used lifetime work history calendars. The other studies used most recent or current job to assign exposure. All studies investigated any exposure to mineral dust with respiratory symptoms and chronic bronchitis, whilst only two studies also assessed cumulative exposure to mineral dust (19, 103). Definition of chronic bronchitis also varied between studies, only one study (100) used a combination of cough and phlegm symptoms of more than three months in the last two years, while other studies defined chronic bronchitis as either cough or phlegm in the last 1-year.

Three studies assessed symptoms of a cough, phlegm, and dyspnea but did not find a significant association with mineral dust exposure (19, 83, 107). Six studies found a significant association with any exposure to mineral dust and chronic bronchitis (23, 100, 102-104, 106) but one Australian study did not detect any association (19). The study that did not find an overall significant association, however, found an increased risk of chronic bronchitis due to mineral dust exposure in women. This study also investigated the weighted cumulative exposure duration and found a dose-response relationship between cumulative exposure to mineral dust and chronic bronchitis, again in women but not in men. In contrast, a recent study from New Zealand also investigated the effect of weighted cumulative exposure and found no relationship between cumulative exposure to mineral dust and chronic bronchitis (103).

Overall, no clear evidence was found to support an association between mineral dust exposure and respiratory symptoms. There was better evidence for an association with chronic bronchitis, however, these studies also had limitations. They used an inconsistent definition of chronic bronchitis, and except for one study, all studies used the current job to assign exposure. The null association with respiratory symptoms may be associated with self-

reported outcomes and use of current job rather than lifetime work history to investigate occupational exposure.

Table 2.5: Population-based studies investigating the association between mineral dust and respiratory symptoms and chronic bronchitis

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of job	Definition used	Any exposure OR(95%CI)	Cumulative exposure (years) OR(95%CI)
Cross-sectional studies							
Hansell et al.(2014) (103)	New Zealand	1,017	ALOHA JEM	Lifetime WHC	CB:cough & sputum≥3months/yr≥1 yr	H=1.87(0.91-3.80) L=2.04(1.06-3.93)	1.87(0.84-4.20)
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	CMH:sputum≥3months/yr ≥1yr	H=1.60(1.02-2.52) L=1.39(1.04-1.87)	N/A
Skorge et al. (2009) (107)	Norway	2,312	ALOHA JEM	Last 11 years	Cough	H=1.06(0.5-2.1) L=0.93(0.5-1.7)	N/A
					Phlegm	H=0.55(0.3-1.0) L=0.64(0.4-1.0)	N/A
					Dyspnea	H=1.11(0.6-2.1) L=1.21(0.7-2.1)	N/A
LeVan et al. (2006) (100)	Singapore	52,325	SR	Current and previous job	CB: chronic cough, phlegm≥3months/yr≥2yrs	1.26 (1.01-1.57)	N/A
					CMH: cough/phlegm	1.08 (0.95-1.22)	
Matheson et al. (2005)(19)	Australia	1,213	ALOHA JEM	Lifetime WHC	CB:phlegm≥3months/yr≥2 yrs	0.59 (0.17-2.08) men	1.48(0.41-5.26)
					CB	3.6(1.06-12.3) women	4.23(1.13-15.8)
					Cough	1.08(0.71-1.65)	N/A
					Dyspnea	1.22(0.89-1.67)	N/A
de Meer et al. (2004)(106)	The Netherlands	1,906	JEM	Current job	CB: cough & phlegm≥3months/yr≥1 yr	2.22(1.16-4.23)	N/A
					Wheeze	1.29(0.95-1.75)	
Sunyer et al.(1998) (83)	Spain	1,735	ALOHA JEM	Current job	Cough	H=1.4(0.8-2.5) L=1.2(0.8-1.9)	N/A
					Phlegm	H=1.0(0.6-1.7) L=0.8(0.5-1.1)	N/A
Heederik et al. (1989) (102)	The Netherlands	828	JEM	Longest job	CB: doctors' diagnosis	OR=1.38 for CB	N/A
					Dyspnea	OR=1.35 for dyspnea	
Cohort study							
Heederik et al. (1990) (23)	The Netherlands	804	JEM	Longest job	CNSLD: doctors' diagnosis	1.58(1.01-2.49)	N/A

Definition of abbreviations: CB= Chronic Bronchitis; CI= Confidence Interval; CMH= Chronic Mucus Hypersecretion; CNSLD= Chronic Non Specific Lung Disease; H=High Exposure; L=Low Exposure; N/A= Not Available; OR=Odds Ratio; WHC= Work History Calendar; SR=Self-Reported

2.6.2.3 Association between mineral dust exposure and COPD

Eight studies have assessed the association between mineral dust exposure and airflow obstruction and they are summarized in Table 2.6. Six studies were cross-sectional (19, 83, 85, 103, 104, 110) and two were cohort studies (20, 84). The findings from the population-based studies were inconsistent. Only three studies (19, 103, 110) used lifetime work history, and two studies used post-BD spirometry to measure fixed AO and to define COPD (103, 110).

The recent Dutch study comparing two cohorts found a significant association with both high and low exposure to mineral dust and AO in the LifeLines cohort, but no association was observed in the Vlagtwedde-Vlaardingen verification cohort (85). The reason for this inconsistent finding in this Dutch study could be related to the smaller sample size in the Vlagtwedde-Vlaardingen cohort (n=2,364), compared with LifeLines cohort (n=11,851). Another Dutch study reported no association with mineral dust exposure in participants with AO; however, they have found an association with mineral dust exposure in participants without AO (104). Surprisingly, the association found in this study between mineral dust exposure and participants without AO only present in people aged less than 50 years but no association was detected in people aged more than 50 years. A Swiss cohort study, however, found no association between high and low exposure to mineral dust and COPD but found a significant association with more severe AO ($FEV_1/FVC<0.7$ and predicted $FEV_1<80\%$) (20). Three studies found no association between cumulative exposure to mineral dust and AO (19, 103, 110), while one cohort study observed a significant association between cumulative years of exposure to mineral dust with AO (20).

Overall, findings from studies that investigated the association between mineral dust exposure and COPD remains unclear. Most studies reported no association between mineral dust and AO, where most of the studies used current job to assign exposure and pre-BD to define AO rather than fixed type of AO. The use of current job and pre-BD may be underestimating the overall effect of mineral dust exposure on AO.

Table 2.6: Population-based studies investigating the association between mineral dust exposure and COPD

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of job	Definitions used	BD	Any exposure OR(95%CI)	Cumulative exposure (years) OR(95%CI)
Cross-sectional studies								
Tagiyeva et al. (2016) (110)	UK	328	JEM	Lifetime WHC	FEV_1/FVC< LLN	Post	1.45(0.74-2.81)	No association
Hansell et al.(2014) (103)	New Zealand	1,017	ALOHA JEM	Lifetime WHC	FEV_1/FVC<LLN	Post	H=0.96(0.43-2.16) L=1.38(0.68-2.80)	1.11(0.46-2.65)
de Jong et al. (2014) (85)	The Netherlands	11,851	ALOHA plus JEM	Current job	FEV_1/FVC<0.7	Pre	H=1.46(1.11-1.92) L=1.19(1.03-1.37)	N/A
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	FEV_1/FVC<0.7	Pre	H=1.01(0.47-2.17) L= 1.18(0.75-1.85)	N/A
Matheson et al. (2005)(19)	Australia	1,213	ALOHA JEM	Lifetime WHC	FEV_1/FVC<0.7	Pre-men	0.88(0.37-2.06)	0.71(0.24-2.10)
						women	1.79(0.60-5.29)	1.16(0.14-9.44)
Sunyer et al.(1998)(83)	Spain	1,735	ALOHA JEM	Current job	FEV_1/FVC<0.7	Pre	H=3.0(1.0-9.4) L=1.4(0.5-3.5)	N/A
Cohort studies								
Mehta et al. (2012) (20)	Switzerland	4,267	ALOHA JEM	Current job	FEV_1/FVC<0.7	Pre	H=0.91(0.62-1.32) L=1.19(0.96-1.49)	1.10(1.01-1.20) 1.08(0.98-1.19)
					FEV_1/FVC<LLN			
Sunyer et al. (2005)(84)	Spain	6,481	ALOHA JEM	Current job	FEV_1/FVC<0.7	Pre -men	H=0.66(0.08-5.31) L=1.71(0.52-5.62)	N/A
						women	H=2.86(0.38-21.55) L=0.51(0.07-3.86)	

Definition of abbreviations: BD= Bronchodilator; CI= Confidence Interval; H=High Exposure; L=Low Exposure; LLN= Lower Limit of Normal; N/A= Not Available; OR=Odds Ratio; UK=United Kingdom; WHC= Work History Calendar

2.6.3 Gases/fumes exposure

2.6.3.1 General overview

Exposure to gases and fumes given off by welding and hot surface cutting processes can be found in many occupations. The diverse mixture of gases such as ammonia, chlorine, phosgene, sulfur dioxide, and hydrogen sulfide are released in many industrial processes and can act as a hazardous respiratory irritants (122). Chlorine and ammonia gases dissolve immediately in the mouth, nose, and throat. The inhalation of these gases is easily transferred to the peripheral respiratory tract via alveoli and prolonged exposure may cause several respiratory diseases including bronchitis, fixed AO, and emphysema (123). Some gases and fumes such as nitrogen dioxide do not dissolve quickly and therefore prolonged exposure may cause inflammation to the small airways or lead to fluid accumulation into the lungs (124). Inhalation of certain gases in small amounts for a prolonged period may also initiate chronic bronchitis, COPD, and emphysema (125). Workers in smelting industries particularly those working in the furnace house, are also exposed to varying degree of respiratory irritants. These include gases such as, nitrogen dioxide, sulfur dioxide, and carbon monoxide. Inhalation exposure to these gases is emitted during the handling, smelting, tapping, and crushing of raw materials. The workers involve in the production, transportation, or storage processes may also be expose to hazardous dusts, gases, or fumes (126).

2.6.3.2 Association between gases/fumes and respiratory symptoms, and chronic bronchitis

Several population-based studies have been conducted to investigate the association between occupational exposure to gases/fumes and respiratory symptoms, and chronic bronchitis (Table 2.7). Of the 15 cross-sectional studies that have investigated these associations, nine studies investigated gases/fumes using JEM based exposure assessment, and of those, only two studies used lifetime work history calendars (19, 103). All studies examined any exposure (low or high) to gases/fumes and only three studies examined the effect of cumulative duration of exposure (19, 103, 105). In terms of the definition of chronic bronchitis, only one study used the gold-standard definition of a combination of a cough and phlegm symptoms for more than three months in the last two consecutive years (100). Other studies used alternative definitions such as either cough or phlegm in the last one year.

Two studies found significant associations between any exposure to gases/fumes and symptom of cough (98, 99) and four studies reported significant associations with dyspnea (98, 99, 127, 128). Six studies found significant associations between gases/fumes exposure and chronic bronchitis, and of them, only three studies assigned exposure using the JEM (103, 104, 129). In contrast, one Australian study did not find any significant association between gases/fumes and respiratory symptoms and chronic bronchitis (19). However, they found an association between exposure to gases/fumes and chronic bronchitis in women only but not in men. Similarly, a Spanish ECRHS-I study reported no association between gases/fumes exposure and respiratory symptoms and chronic bronchitis (83). The null association reported in this ECRHS-I study could be related to the relatively younger age of the study population (20 to 44 years) and exposure assignment using the current job rather than lifetime work history calendar.

In summary, there is considerable evidence for an association between occupational exposure to gases/fumes and chronic bronchitis, but the association with respiratory symptoms remains unclear. This inconsistency in the associations with respiratory symptoms may be due to the heterogeneity of self-reported definitions of symptoms. Furthermore, most of the studies used the current job to assign exposure rather than lifetime work history that highlighted further limitations that studies might have been missed previous exposures and therefore, may be affected by healthy worker effect.

Table 2.7: Population-based studies investigating the association between gases/fumes exposure with respiratory symptoms and chronic bronchitis

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of job	Definitions used	Any exposure OR(95%CI)	Cumulative exposure (yrs) OR(95%CI)
Cross-sectional studies							
Hansell et al.(2014)(103)	New Zealand	1,017	ALOHA JEM	Lifetime WHC	CB:cough,sputum≥3months/yr≥ 1 yr	H=2.1(1.11-3.98) L=1.21(0.69-2.13)	1.78(0.92-3.44)
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	CMH:sputum≥3months/yr≥1yr	H=2.19(1.49-3.22) L=1.13(0.87-1.47)	N/A
Lam et al. (2012)(98)	China	8,216	SR	Longest job	Dyspnea	H=1.31(1.09-1.58) L=1.15(0.95-1.41)	N/A
					Cough	H=1.56(1.02-2.37) L=0.86(0.49-1.51)	
Darby et al. (2012)(129)	UK	2,061	JEM	Current job	CB: doctor's diagnosis	2.20 (1.45-3.35)	N/A
Skorge et al. (2009) (107)	Norway	2,312	ALOHA JEM	Last 11 yrs	Cough	H=0.99(0.5-1.9)	N/A
					Phlegm	H=0.67(0.4-1.1)	
					Dyspnea	H=1.47(0.8-2.6)	
Krstev et al. (2008) (105)	China	14,500	SR	Job > 1year	CB: doctor's diagnosis	1.39(0.87-2.24)	1.18(0.52-2.68)
LeVan et al. (2006) (100)	Singapore	52,325	SR	Job > 1year	CB: cough, phlegm ≥3months /yr ≥2yrs	1.26 (1.01-1.57)	N/A
					CMH: cough/phlegm	1.08 (0.95-1.22)	N/A
Matheson et al. (2005)(19)	Australia	1,213	ALOHA JEM	Lifetime WHC	CB: phlegm ≥3months /yr≥2 yrs, - men	1.62(0.42-6.26)	1.93(0.42-8.89)
					women	4.85(1.03-22.9)	5.6(1.10-28.4)
					Cough	1.16(0.79-1.72)	N/A
					Dyspnea	1.09(0.82-1.45)	N/A
de Meer et al. (2004)(106)	The Netherlands	1,906	JEM	Current job	CB: cough, phlegm ≥3months/yr≥1 yr	0.67(0.36-1.26)	N/A
					wheeze	1.14(0.86-1.68)	
Lange et al(2003) (130)	Denmark	3,736	SR	Current job	CMH: phlegm ≥3 months /yr ≥2 yrs	2.2(1.7-2.7)	N/A
Zock et.al. (2001) (131)	Multi-center	12,154	JEM	Current job	CB:cough,phlegm≥3months	1.5(0.9-2.6)	N/A
Sunyer et al.(1998) (83)	Spain	1,735	ALOHA JEM	Current job	Cough,	H=0.9(0.5-1.5) L=1.1(0.8-1.6)	N/A
					Phlegm	H=1.7(1.0-2.9) L=1.1(0.8-1.6)	
Fishwick et al. (1997) (127)	New Zealand	1,609	JEM	Current job	CB: phlegm in the morning	1.2(0.9-1.7)	N/A
					Dyspnea	1.16(1.07-1.27)	
Xu et al. (1992) (128)	China	3,606	SR	NM	CB: cough and phlegm	1.12(1.01-1.23)	N/A
Korn et al. (1987)(99)	USA	8,515	SR	Lifetime WH	Cough, Phlegm	1.36(1.17-1.57), 1.27(1.10-1.47)	N/A
					Wheeze, Dyspnea	1.29(1.08-1.55), 1.43(1.19-1.72)	

Definition of abbreviations: BD= Bronchodilator; CI= Confidence Interval; H=High Exposure; L=Low Exposure; LLN= Lower Limit of Normal; N/A= Not Available; OR=Odds Ratio; SR=Self-Reported; UK=United Kingdom; USA=United States of America; WHC= Work History Calendar

2.6.3.3 Association between gases/fumes exposure and COPD

Several population-based studies have been conducted to investigate the association between occupational exposure to gases/fumes and COPD. Of the 19 studies presented in Table 2.8, 17 studies assessed prevalence and two studies assessed incidence (20, 84). Only two studies collected lifetime occupational history from the participants and therefore, examined the association with cumulative exposure along with any exposure to gases/fumes (19, 103). An acceptable universal definition of COPD is still debated and therefore, of the 19 studies, only two studies (103, 132) used post-BD spirometry to define COPD based fixed AO. In terms of spirometric cut-off criteria, seven studies used GOLD criteria, four studies used the LLN criteria and two studies (20, 132) used both criteria to define fixed AO. Other studies used either physicians' diagnosis (22, 129), a combination of respiratory symptoms (106, 128) and lung function (133) to define AO.

Of the 19 studies, six studies found that any (either high or low or combined) exposure to gases/fumes was associated with increased risk of COPD as most of them used pre-BD spirometry for the definition of COPD. The two studies that used post-BD spirometry to define fixed nature of AO concluded with very different results (103, 132). The study from Sweden found an association between fixed AO and any exposure to gases, or fumes (132), while the study from New Zealand did not find significant association (103). The inconsistent findings were probably the result of the different exposure assessment methods used in these studies. The Swedish study used self-reported exposure, while the study from New Zealand used the ALOHA JEM to assign exposures. Another reason for the inconsistent findings may be associated with the sampling technique used, as the Swedish study was an enriched sample of asthma participants that may have influence the overall association found in this study (132). Two cohorts from Switzerland (20) and the ECRHS (84) that investigated the incidence of COPD with gases/fumes exposure did not find any significant association. However, the Swiss study found an association between high exposure to gases/fumes and more severe COPD. This study also found relationship between cumulative exposure to gases/fumes and COPD (20).

In summary, cross-sectional studies provide adequate evidence that occupational exposure to gases/fumes may increase the risk of AO, but the results from cohort studies did not find any evidence for an association. However, these inconsistencies may be due to the differences in the spirometric definition of COPD (pre-BD vs. post-BD) and the differences in the age of the study populations.

Table 2.8: Population-based studies investigating the association between gases/fumes exposure and COPD

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of jobs	Definitions used	BD	Any exposure OR(95%CI)	Cumulative exposure (years) OR(95%CI)
Cross-sectional studies								
Würtz et al. (2015) (108)	Denmark	1,575	SR	NM	$FEV_1/FVC<LLN$	Pre	3.69(1.36-10.04)	N/A
Hagstad et al.(2015) (132)	Sweden	1,604	SR	Current job	$FEV_1/FVC<0.7$	Post	1.85(1.03-3.33)	N/A
Würtz et al. (2014) (109)	Denmark	4,717	SR	NM	$FEV_1/FVC<LLN$	Pre	H=1.38(0.99-1.93) L=1.05(0.61-1.80)	N/A
Hansell et al.(2014)(103)	New Zealand	1,017	ALOHA JEM	Lifetime WHC	$FEV_1/FVC<LLN$	Post	H=0.85(0.39-1.85) L=1.01(0.56-1.81)	0.93(0.43-1.88)
de Jong et al. (2014) (85)	The Netherlands	11,851	ALOHA plus JEM	Current job	$FEV_1/FVC<0.7$	Pre	H=1.44(1.16-1.80) L=1.10(0.98-1.24)	N/A
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	$FEV_1/FVC<0.7$	Pre	H=0.98(0.49-1.94) L= 1.04(0.70-1.54)	N/A
Lam et al. (2012) (98)	China	8,216	SR	Longest job	$FEV_1/FVC<LLN$	NM	H=1.48(1.03-2.12) L=1.41(0.95-2.10)	N/A
Darby et al. (2012) (129)	UK	2,061	JEM	Current job	Doc diagnosis	NM	0.88(0.58-1.34)	N/A
Jaén et al. (2006) (133)	Spain	576	SR	Lifetime WHC	FEV_1/FVC (%)	Pre	-1.1(-2.3 to 0.1)	-1.7(-3.3 to -0.2)
Matheson et al. (2005)(19)	Australia	1,213	ALOHA JEM	Lifetime WHC	$FEV_1/FVC<0.7$	Pre - men	1.19(0.49-2.92)	1.03(0.37-2.92)
						women	2.37(0.85-6.60)	1.39(0.49-3.94)
de Meer et al. (2004)(106)	The Netherlands	1,906	JEM	Current job	Symptoms	NM	N/A	N/A
Trupin et al. (2003) (22)	USA	2,061	JEM	Current job	Physicians diagnosis	NM	H=1.6(1.1-2.5) L=1.4(1.1-1.9)	N/A
Zock et.al. (2001) (131)	Multi-center	12,154	JEM	Current job	Not defined	NM	1.0(0.8-1.3) in current smoker	N/A
Sunyer et al.(1998) (83)	Spain	1,735	ALOHA JEM	Current job	$FEV_1/FVC<0.7$	Pre	H=0.8(0.2-3.0) L=1.5(0.6-3.5)	N/A
Fishwick et al. (1997) (127)	New Zealand	1,609	JEM	Current job	$FEV_1/FVC<0.75$	Pre	1.2(0.7-1.8)	N/A
Xu et al. (1992) (128)	China	3,606	SR	NM	Symptoms	NM	1.12(1.01-1.23)	N/A
Korn et al. (1987)(99)	USA	8,515	SR	Lifetime WHC	$FEV_1/FVC<0.6$	Pre	1.15(0.87-1.51)	N/A
Cohort studies								
Mehta et al. (2012) (20)	Switzer-land	4,267	ALOHA JEM	Current job	$FEV_1/FVC<0.7$	Pre	H=1.00(0.70-1.42) L=1.05(0.88-1.26)	1.10(1.02-1.19) 1.06(0.98-1.15)
					$FEV_1/FVC<LLN$			
Sunyer et al. (2005)(84)	Spain	6,481	ALOHA JEM	Current job	$FEV_1/FVC<0.7$	Pre-men	H=0.44(0.05-3.50) L=0.83(0.25-2.77)	N/A
						women	L=1.00(0.35-2.83)	

Definition of abbreviations: BD= Bronchodilator; CI= Confidence Interval; H=High Exposure; L=Low Exposure; LLN= Lower Limit of Normal; N/A= Not Available

2.6.4 Pesticides exposure

2.6.4.1 General overview

Pesticides is the term used to describe a range of chemicals including insecticides, fungicides, herbicides, and rodenticides. Pesticides are widely used chemical substances in the occupational setting as well as in household work. Pesticides are mainly used in agriculture, forestry, fishery and food industry to control the pests and pest-induced diseases. Occupational exposure to pesticides depends on their application, intensity, frequency, duration of use and implementation, use of safety barriers and the physiochemical and toxicological properties of the pesticides. Additionally, accidental spills or incorrect use of pesticides, leakages, non-compliance with safety guidelines can lead to pesticide exposure (134).

Inhalation is the main route of entry for pesticides to the respiratory tract, in particular for those working without respiratory protection. Subjects can be exposed to pesticides during mixing, preparation, fumigation, and application to crops. However, depending upon the industry, exposure can also occur during manufacture, storage, or transport (135, 136). Long-term exposure to organophosphate pesticides inhibits acetylcholinesterase synthesis leading to mucus hypersecretion and airway smooth muscle contraction causing breathlessness, cough, and wheeze (136).

2.6.4.2 Different types of pesticides

Based on the target, pesticides are mainly categorized into herbicides, insecticides, fungicides, bactericides, rodenticides, nematicide, acaricide, and fumigants (135). Pesticides can also be classified into organochlorines, organophosphates, carbamates, dithiocarbamates, pyrethroids, phenoxyl, triazine, amide, and coumadin compounds based on their chemical properties. Other substances such as urea derivatives, sulfur fumigants and even several biological products have also been used as pesticides (134). Organophosphate insecticides are used on a variety of crops and also used around the home and garden to control insects. Pyrethrums and synthetic pyrethroids are usually less toxic pesticides that have replaced many of the old commonly used organophosphates. Pesticides can be classify based on their

mechanism of action. Organochlorines, organophosphates are recognized as neurotoxins, while phenoxyl herbicides are planting hormone analogs. Some forms of pesticides such as triazine and urea herbicides interact with the metabolic and physiological process of plants. Amide herbicides disrupt energy production from the body and act as an inducer of oxidative stress (134). Some common types of pesticides are listed below in Table 2.9.

Table 2.9: Commonly used pesticides and their chemical name

Types of pesticides	Chemicals
Herbicides	Chlorophenoxyl, urea derivatives, triazines, amide, bipyridils (paraquat), glyphosate
Insecticides	Organochlorines, chlorinated cyclohexanes and benzenes, cyclodienes and chlordecone, organophosphates, carbamates, pyrethroids, rotenone, Bacillus thuringiensis
Fungicides and bactericides	Dithiocarbamate, captan, captofol, pentachlorophenol, iprodione, sulphur
Rodenticides	Coumadin and derivatives, anticoagulants, strychnine, sodium fluoroacetate
Fumigants	Methyl bromide, aluminum/zinc phosphide, sulfur

2.6.4.3 Pesticides exposure in Australia

Since 1950, organochlorine insecticides were commonly used in Australia and were subsequently replaced by the organophosphate insecticides during the 1970s and 1980s. Pesticides and pesticide related products have increased in usage in Australia by 7 to 30% since 2000 (137). Increased use of herbicides, insecticides, and fungicides in agriculture and farming has led to both occupational as well as environmental exposure (137). The recent Australian Work Exposures Study reported that around 4% of Australian male workers were exposed to pesticides (137). In this study, workers were mainly involved with mixing and the application of pesticides. The increased prevalence of pesticides exposure was mainly associated with agriculture, animal husbandry, horticulture, and forestry (137). Another Nationwide cross-sectional survey of 1,197 Australian female veterinarians found that 54% of the workers exposed to pesticides were working at least 45 hours per week (138). This study also found that 43% of veterinarians were exposed to pesticides on either a weekly or a daily basis. However, this study was conducted among a selective working population and used self-reported exposure that may lead to differential exposure misclassification.

2.6.4.4 Association between pesticides and respiratory symptoms, and chronic bronchitis

The evidence for the association between occupational exposure to pesticides and respiratory symptoms and chronic bronchitis have been derived from workplace-based studies. To date, no population-based studies have been conducted so far to investigate this association, which is a major limitation in the current literature exploring the relationship between occupational exposure to pesticides and respiratory symptoms and chronic bronchitis.

Workplace studies have reported a higher prevalence of respiratory symptoms among workers exposed to pesticides (summarized in Table 2.10). Cough, phlegm, wheeze, dyspnea, chest tightness are common respiratory symptoms found to be associated with pesticide exposure (134). A cross-sectional study in a bottling plant reported that, in comparison to controls, pesticide workers had an increased risk of developing respiratory symptoms, including a chronic cough, dyspnea, throat irritation, and nasal dryness. Additionally, cough, wheezing, chest tightness, and dyspnea were increased across the work-shift among pesticide workers (139). Another study of livestock farmers demonstrated that pesticide exposures were associated with an increased risk of phlegm and wheeze, after controlling for age and smoking. The results of this study may have been affected by concurrent exposures to other environmental agents (140). An Iranian workplace-based study reported that sheep farmers had an increased risk of wheezing and phlegm compared to agriculture farmers (141). Another study from the Farm Family Health and Hazard Surveillance Program (FFHHSP) among grain farmers in the US reported that chronic cough was significantly associated with pesticide exposure (142). A recent study among commercial farmers also concluded that workers exposed to pesticides were at risk of developing respiratory symptoms and lower lung function (143). Workforce based studies have also found significant associations with poor lung function and respiratory symptoms in occupations exposed to pesticides such as agriculture workers (131, 144) and farmers (145, 146). Evidence from a recently conducted systematic review suggested an association between pesticide exposure and respiratory symptoms (135).

However, all of these studies were solely based on specific occupational groups, some of them were in developing countries and, therefore, results may not be generalizable to the general population.

Table 2.10: Workplace-based studies investigating the association between pesticides exposure and respiratory symptoms and chronic bronchitis

First author (year)	Location	Methods of exposure assessment	Outcomes	Findings OR (95% CI)
Negatu et al. (2016) (143)	Ethiopia	Questionnaire	Cough	3.15(1.56-6.36)
			Phlegm	2.02(0.58-7.01)
			Wheeze	3.16(0.96-10.47)
			Dyspnea	6.67(2.60-17.58)
Chakraborty et al. (2009) (144)	India	Questionnaire, workers exposed to at least one hour a day five days a month for past five years	CB	4.1(2.2-6.3)
			Cough	3.2(2.4-4.3)
			Dyspnea	3.7(2.7-4.8)
			Wheeze	2.9(2.1-4.2)
Zuskin et al. (2008) (139)	Croatia	Questionnaire	Cough	0.98(0.86-1.11) men
				1.29(1.15-15.84) women
			Dyspnea	2.35(1.50-4.10) men
				1.11(1.06-1.97) women
Hoppin et al. (2007) (146)	USA	Questionnaire on lifetime job	CB	CB=1.85(1.51-2.25)
Hashemi et al. (2006) (141)	Iran	Questionnaire	Cough	1.6(0.7-3.9)
			Phlegm	2.2(0.5-10.5)
			Wheeze	2.6(0.6-12.2)
			Dyspnea	3.5(1.2-9.98)
Faria et al. (2005) (145)	Brazil	Questionnaire and pesticide application >2 days/month versus no exposure	Asthma	Not reported
Sprince et al. (2000) (140)	USA	Questionnaire	Cough	p=0.000
			Phlegm	p=0.29
			Dyspnea	p=0.001
			CB	p=0.001
Wilkins et al. (1999) (142)	USA	Questionnaire	Cough	0.75(0.28-2.04)
			Phlegm	0.65(0.29-1.45)
			Dyspnea	0.93(0.43-2.03)
			CB	0.87(0.29-2.64)

Definition of abbreviations: CB= Chronic Bronchitis; CI= Confidence Interval; OR=Odds Ratio; USA=United States of America

2.6.4.5 Association between pesticide exposures and COPD

Workplace-based studies also suggest an association between pesticide exposure and COPD (144, 147) but the evidence from the population-based studies is scant. To date, only one population-based study has investigated the association between pesticide exposure and AO using two similar types of cohorts in the Netherlands but the results were largely inconsistent across the subcategories of pesticides exposure and between the two cohorts as well (85) (Table 2.11). This study used the ALOHA plus JEM to assign exposure and categorized the exposures into all pesticides, herbicides, and insecticides. In this Dutch cohort study, high exposure to pesticides was significantly associated with AO in the Vlagtwedde-Vlaardingen cohort and high exposure to herbicides was associated with AO in the LifeLines cohort. They found consistent associations between all subgroups of all pesticides and poorer lung function (FEV_1) in the LifeLines cohort (85). The magnitude of the association in this study, particularly with herbicides exposure, was of greater or similar magnitude to that observed for dusts, gases, and fumes and suggested a dose-response relationship, but no information on cumulative exposure was reported.

Pre-BD spirometry was used in this study to define AO, which may have overestimated the risk observed in this study (34). Furthermore, it did not allow for the assessment of fixed AO. Survivor bias may have affected the results since participants already affected by respiratory symptoms at the time of their job may have changed jobs or changed their work environment to reduce their level of exposure. Therefore, those participants would not be classified as having had pesticide exposure. By using, most recent or current job, the authors would have missed previous occupational exposures, which may have influence the overall risk of AO (91).

Despite the challenges and limitations, this study provides some evidence that occupational exposure to the pesticide was associated with AO defined by pre-BD spirometry and lung function. However, above results suggests that more population-based studies with phenotype assessment of COPD particularly fixed nature of AO, are needed to clarify the role of pesticides exposure on respiratory health.

Table 2.11: Population-based studies investigating the association between pesticide exposures and COPD

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of jobs	Definition used	BD	Exposures	OR(95%CI)	β (95%CI) with FEV_1 (mL)
Cross-sectional study									
de Jong et al. (2014) (85)	The Netherlands	11,851	ALOHA plus JEM	Current job	$FEV_1/FVC<0.7$	Pre	Pesticides	**LifeLines cohort**	
								H=1.28(0.79-2.09) L=0.83(0.60-1.14)	H= -113(-201,-25) L= -51(-102,0)
								Vlagtwedde-Vlaardingen cohort	
								H=1.48(1.04-2.10) L=1.33(0.87-2.01)	N/A
							Herbicides	**LifeLines cohort**	
								H=2.11(1.03-4.30) L=1.04(0.65-1.67)	H= -204(-350,-58) L= -59(-140, 22)
								Vlagtwedde-Vlaardingen cohort	
								H=1.36(0.93-2.00) L=1.29(0.85-1.98)	N/A
							Insecticides	**LifeLines cohort**	
								H=1.32(0.81-2.16) L=0.81(0.58-1.15)	H= -109(-197, -21) L= -50(-105, 5)
								Vlagtwedde-Vlaardingen cohort	
								H=1.39(0.98-1.98) L=1.04(0.64-1.70)	N/A

Definition of abbreviations: CI= Confidence Interval; H=High Exposure; L=Low Exposure; JEM=Job Exposure Matrix; β= Linear coefficient, OR=Odds Ratio; N/A=Not Available

2.6.5 Solvents exposure

2.6.5.1 General overview

Solvents (organic) are defined by the presence of hydrocarbon (at least one carbon atom and one hydrogen atom) in their molecular structure and are characterized by their low molecular weight, high volatility and lipophilic nature (148). As most solvents are highly volatile they rapidly evaporate into the workers breathing zone where they enter the respiratory tract through inhalation. Inhalation of solvents (organic) has been shown to slowly damage the central and peripheral airways causing mucus hypersecretion primarily in the large airways and gradually involving the small airways in the later stages resulting in COPD (104).

Solvents are commonly used in industrial processes, in homes, or in offices. They are used for extraction of fats and oils, degreasing, dry cleaning, and the manufacturing of a wide range of products including printing inks, paints and cleaning products (148, 149). Although solvents have been used effectively in many different workplaces, they have, however, many adverse health effects. The main health effects that have been well documented in the literature are central nervous system toxicity, dermatitis, liver, renal damages, respiratory effects, and cancer (150). Workers exposed to solvents, often complain of respiratory symptoms including cough, phlegm, chest tightness, and shortness of breath that may lead to the subsequent development of COPD and lung function decline. However, surprisingly there is very little evidence from population-based studies on solvents exposure and their relationship with COPD and lung function decline despite findings from workplace-based studies that these exposures may be a causal relationship with COPD and lung function (150).

2.6.5.2 Categories of solvents

Solvents (organic) are categorized according to their chemical structure. The common classes of organic solvents are aliphatic, cyclic, aromatic, and halogenated hydrocarbons. Aliphatic hydrocarbons may contain either one or more saturated or unsaturated hydrocarbons that contain one or more double (alkenes) or triple (alkynes) bonds. Cyclic hydrocarbons are saturated or unsaturated hydrocarbon rings that contain three or more atoms in their molecular structure. Petroleum solvents usually contain cyclic compounds and also

include gasoline, diesel fuel, mineral spirits and kerosene. Aromatic solvents include coal-derived hydrocarbon that is characterized by one or more benzene rings (six-carbon ring) in their molecular structure. Halogenated hydrocarbons are usually saturated and unsaturated hydrocarbons that contain one or more halogen compound such as chlorine, fluorine, bromine, or iodine in their molecular structure (150).

Chlorinated solvents use halogenated hydrocarbons containing chlorine atoms in their molecular structure that belong to the halogenated hydrocarbons family (150, 151). They are commonly used for commercial purposes due to their excellent ability to dissolve oils together with non-flammable characteristics. They are also used in different commercial processes including cleaning products and degreasers for textiles and metals. Chlorinated solvents are considered highly toxic substances, as long-term inhalation of chlorinated solvents may cause depression of central nervous system, damage to the lungs, heart, kidney, or liver as well as skin irritation (151). However, the health effect due to exposure to chlorinated solvents depends on the level of exposure and on the specific type of the solvent.

In addition to the main solvents described above, there are other types of solvents containing oxygen atoms in their molecular structure. These are commonly derived from the fermentation of agricultural products, such as ethanol and esters. These oxygenated solvents are also classified into several families based on their chemical structure, as is shown below in Table 2.12.

Table 2.12: Solvents (organic) families

Types of solvents	Example
Aliphatic hydrocarbons	Methane, ethane, propane, butane, etc
Cyclic hydrocarbons	Gasoline, cyclohexane
Aromatic hydrocarbons	Benzene, toluene, polycyclic aromatic hydrocarbons
Halogenated hydrocarbons	Chlorinated solvents • Chlorinated methanes (chloromethane, dichloromethane, trichloromethane, tetrachloromethane) • Chlorinated ethanes (trichloroethane) • Perchloroethylene, trichloroethylene, chloroform, carbon tetrachloride
Alcohols	Ethanol, methanol, isopropanol, n-butanol
Ketones	Acetone, methyl ethyl ketone, methyl isobutyl ketone
Esters	Ethyl acetate, n-propyl acetate, n-butyl acetate
Ethers	Diethyl ether, tetrahydrofuran (THF)
Glycols Ethers	Ethylene glycol

2.6.5.3 Association between solvents and respiratory symptoms, and chronic bronchitis

Evidence from population-based studies has suggested that occupational exposure to solvents (organic) may be associated with respiratory symptoms and chronic bronchitis (summarized in Table 2.13). Most population-based studies examined this association using self-reported questionnaire-based exposure assessment and few studies used JEM to assess exposure. Of the eight published studies that assessed the relationship between organic solvents and chronic bronchitis, six were cross-sectional (100-102, 104, 152, 153) and two were cohort studies (23, 24). More than half of the studies used self-reported or doctors' diagnosis to define chronic bronchitis, but none of the studies used lifetime work history. Therefore, none could establish any relationship between cumulative solvents exposure and respiratory symptoms and chronic bronchitis.

A recent cross-sectional study from the Netherlands investigated the possible association using the ALOHA plus JEM and solvents categorized into aromatic solvents, chlorinated solvents, and other solvents (104). This is the only study that specifically examined different types of solvents in a population-based study. In this study, high exposure to aromatic solvents and chlorinated solvents were significantly associated with chronic mucus hypersecretion which was defined as the presence of sputum for more than three months for more than one-year. However, the association reported in this study was only present in participants without COPD. A limitation of this study was the use of most recent or current job to assign exposures and did not examine cumulative exposure effect. Another study from the Netherlands examined the incidence of chronic nonspecific lung disease using a JEM along with lifetime work history and found a significant association with overall solvents (24). Two other major European studies reported a significant association between overall solvents exposure and chronic bronchitis, although both of these studies used a self-reported questionnaire to assign exposure (101, 152). In contrast, two cross-sectional (100, 102) and one cohort study (23) did not find a significant association between exposure to solvents and chronic bronchitis. The reason for the null association in these studies could be related to their smaller sample size that limits the ability to detect an association.

In general, solvents (organic) have been found to be associated with chronic bronchitis, but studies of respiratory symptoms have been limited and inconsistent. There is also limited evidence for an association between subgroups of solvents, such as aromatic solvents and chlorinated solvents, and respiratory symptoms and chronic bronchitis. Further research is needed to clarify the role of these solvents on respiratory symptoms and chronic bronchitis.

Table 2.13: Population-based studies investigating the association between solvents (organic) exposure and respiratory symptoms and chronic bronchitis

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of jobs	Definitions used	Solvents assessed	Any exposure OR(95%CI)
Cross-sectional studies							
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	CMH:sputum≥3months/yr ≥1 yr	Aromatic solvents	H=1.43(1.00-2.07) L=1.68(0.65-4.30)
						Chlorinated solvents	H=1.98(1.00-3.90) L-1.46(0.96-2.22)
						Other solvents	H=1.29(0.26-6.5) L=0.58(0.27-1.27)
Ebbehoj et al. (2008) (152)	Denmark	3,387	SR	Jobs>5 years	CB: chronic cough, phlegm≥3months/yr≥2yrs	Overall solvents	1.6(1.1-2.5)
LeVan et al. (2006) (100)	Singapore	52,325	SR	Jobs>1 year	CB: chronic cough, phlegm≥3months/yr≥2yrs CMH: cough/phlegm	Chemical solvents	CB: 1.02(0.71-1.45) Cough:1.63(1.17-2.27) Phlegm:1.20(1.05-1.37)
Suadicani et al. (2001) (101)	Denmark	3,387	SR	Jobs>5 years	CB: chronic cough, phlegm≥3months/yr≥2yrs	Overall solvents	1.5(1.1-2.1)
Heederik et al. (1989) (102)	The Netherlands	828	JEM	Longest job	CB: doctors' diagnosis CNSLD	Overall solvents	OR=0.82 for CB OR=2.72 for CNSLD
Lebowitz et al. (1977) (153)	USA	1,195	SR	Jobs>6 months	Cough, wheeze	Overall solvents	PRR=18.6 cough PRR=11.8 wheeze
Cohort studies							
Heederik et al. (1990) (23)	The Netherlands	804	SR	Longest job	CB: doctors' diagnosis	Overall solvents	1.16(0.7-1.94)
Post et al. (1994) (24)	The Netherlands	804	JEM	Lifetime WHC	CNSLD:doctors' diagnosis	Overall solvents	1.73(1.14-2.62)

Definition of abbreviations: CB= Chronic Bronchitis; CMH= Chronic Mucus Hypersecretion; CNSLD=Chronic Non Specific Lung Disease; CI= Confidence Interval H=High Exposure; L=Low Exposure; OR=Odds Ratio; PRR=Prevalence Rate Ratio; SR=Self-Reported; USA=United States of America; WHC= Work History Calendar

2.6.5.4 Association between exposure to solvents (organic) and COPD

As described in the previous section, specific solvents were found to be associated with AO in several workplace-based studies, but there is limited and inconsistent evidence from population-based studies (presented in Table 2.14). The reason for the inconsistency between studies may be related to the exposure assessment method used and the lack of use of a standardized definition of COPD using post-BD spirometry. All studies that investigated the association with solvents (organic) and COPD used pre-BD spirometry and none examined the effect of cumulative exposure.

The Dutch LifeLines cohort study reported that low exposure to aromatic solvents and chlorinated solvents were significantly associated with AO and poor lung function (85). However, this study was conducted in a rural region of the Netherlands where the majority of participants were involved in blue-collar jobs that may influence the association found in this study. Another study conducted within the same cohort did not find a significant association, but they reported an interaction effect between aromatic solvents and chlorinated solvents with COPD when they stratified the results based on cases of COPD (104). The null association in this study could be related to the small number of participants with COPD that may have limited the power to detect an association, and the results were very different from the previous Dutch study. Another two studies reported an increased risk of COPD due to solvents exposure (153, 154).

Overall, the evidence for an association between solvents and COPD is limited and inconsistent. Furthermore, few studies have been conducted to date, and none of the studies have used lifetime occupational history with post-BD spirometry to assess this relationship, which is a major limitation in the current literature.

Table 2.14: Population-based studies investigating the association between solvents (organic) exposure and COPD

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of jobs	Definitions used	BD	Solvents assessed	Any exposure OR(95%CI)
Cross-sectional studies								
de Jong et al. (2014) (85)	The Netherlands	11,851	ALOHA plus JEM	Current job	$FEV_1/FVC<0.7$	Pre	Aromatic solvents	H=0.92(0.48-1.75) L=126(1.04-1.52)
							Chlorinated solvents	H=1.38(0.91-2.10) L=1.09(0.87-1.36)
							Other solvents	H=0.99(0.65-1.50) L=1.04(0.91-1.18)
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	$FEV_1/FVC<0.7$	Pre	Aromatic solvents	H=0.75(0.09-6.47) L=0.69(0.36-1.33)
							Chlorinated solvents	H=0.44(0.10-2.03) L=0.94(0.45-1.96)
							Other solvents	H=1.78(0.61-5.23) L=1.10(0.61-5.23)
Le Moual et al. (1994) (154)	France	10,046	JEM	Current job	Lung function	Pre	Overall organic solvents	P<0.01
Lebowitz et al. (1977) (153)	USA	1,195	SR	Jobs>6 months	Lung function	Pre	Overall organic solvents	PRR=11.3

Definition of abbreviations: BD=Bronchodilator; CI= Confidence Interval; H=High Exposure; L=Low Exposure; JEM= Job Exposure Matrix; OR=Odds Ratio; PRR=Prevalence Rate Ratio; SR=Self-Reported; USA=United States of America

2.6.6 Metals exposure

2.6.6.1 General overview

Metals are widely used in industrial processes and represent an important hazardous respiratory irritant in the workplace (155). Steelworkers, automobile workers, tunnel workers, hard rock miners, and welders in the steel, petrochemical, or mining industries are potentially exposed to heavy metals. Previous workplace based studies have also demonstrated that steel workers (155), tunnel workers (156), welders (113) and hard metal workers (157) are occupationally exposed to metals. A recent systematic review also suggested that welding fumes exposure was associated with accelerated decline in lung function (158). The highly volatile and toxic compound "osmium" may result in severe acute lung inflammation following inhalation exposure (159). Another lung irritant, "vanadium" that is released during oil and coal combustion and from metallurgic work is also a hazardous substance to the lungs (160). A workplace based study found that vanadium pentoxide is associated with increased incidence of chronic bronchitis (161). Cadmium is a by-product of zinc production that is usually used for electroplating and battery production. Common occupational exposure to cadmium may result from mining, metallurgy, fossil fuel combustion, and from iron, steel and cement production (162). Inhalation of cadmium may be responsible for alveolar cell damage that leads to the development of emphysema (163). Metals recognized as toxic to humans include lead, mercury, arsenic, and cadmium. Some metals are essential for human biochemical processes and act as important cofactors for several enzymatic processes. Vitamin B-12 contains cobalt atom in its core; and hemoglobin contains iron. These are essential trace elements in the human body. Copper, manganese, and chromium are also essential trace elements in the human diet (164). The toxicity of metals depends on the dose absorbed, and whether the exposure was acute or chronic. The age of individuals also influences the metal toxicity, for example, lead toxicity is common in children; while mercury, cadmium and arsenic toxicity are usually chronic and mostly affect adults. Exposure to metals may also occur through the diet, medications, occupation, and from the environmental exposure. For that reason, a full occupational, dietary and lifestyle history need to be considered to diagnose hidden source of metal exposure (164).

2.6.6.2 Association between metals and respiratory symptoms, and chronic bronchitis

Although there is some evidence from population-based studies that occupational exposure to metals is associated with respiratory symptoms and chronic bronchitis, the current literature is limited by using self-reported exposure assessment and differences in the definition of chronic bronchitis. Three cross-sectional studies (100, 102, 104) and one cohort study (23) investigated the relationship between metals exposure with chronic bronchitis (Table 2.15). All studies assessed exposure using the metric "any" exposure to metals, but no studies assessed cumulative exposure. A recent Dutch cohort study used ALOHA plus JEM to assign exposure and examined the relationship with chronic mucus hypersecretion. They reported an association with high exposure to metals, in participants without AO (104). Another study from the Netherlands found a similar association with heavy metals exposure, although they relied on doctors' diagnosis to define chronic nonspecific lung disease (23). In contrast, two studies from the Netherlands (102) and Singapore (100) did not find a significant association between metals exposure and chronic bronchitis. However, the lack of a positive finding in these two studies may be due to the self-reported occupational exposure. One study used JEM (102) and defined chronic bronchitis based on doctors' diagnosis, while the other study used a self-reported method to assign occupational exposure (100).

Overall, findings from the studies summarized above suggest a link between metals exposure and chronic bronchitis. However, further studies are necessary using lifetime work history to clarify the role of metal exposure in chronic bronchitis and respiratory symptoms.

Table 2.15: Population-based studies investigated the association between metals exposure with respiratory symptoms and chronic bronchitis

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of jobs	Definitions used	Any exposure OR(95%CI)
Cross-sectional studies						
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	CMH:sputum⩾3months/yr⩾1yr	H=2.26(1.30-3.94) L=1.070.65-1.76)
LeVan et al. (2006) (100)	Singapore	52,325	SR	Jobs>1 year	CB: chronic cough, phlegm≥3months/yr ⩾2yrs	1.04(0.74-1.45)
					CMH: cough/phlegm	1.09(0.95-1.25)
Heederik et al. (1989) (102)	The Netherlands	828	JEM	Longest job	CB: doctors' diagnosis	OR=1.65
Cohort study						
Heederik et al. (1990) (23)	The Netherlands	804	JEM	Longest job	CNSLD: doctors' diagnosis	2.15(1.23-3.77)

Definition of abbreviations: CB= Chronic Bronchitis; CMH= Chronic Mucus Hypersecretion; CNSLD=Chronic Non Specific Lung Disease; CI= Confidence Interval; H=High Exposure; L=Low Exposure; JEM= Job Exposure Matrix; OR=Odds Ratio; SR=Self-Reported

2.6.6.3 Association between exposure to metals and COPD

Epidemiological studies that have investigated the effect of occupational exposure to metals on COPD have produced inconsistent results (summarized in Table 2.16). Only two cross-sectional studies have reported this relationship. The Dutch cohort study assessed this association in participants with COPD but did not find any significant associations between high and low exposure to metals and airflow obstruction (104). In this study, current job was used to assign exposures, and it is likely that this study may have underestimated the true impact of metals exposure on COPD. Survivor bias may have affected these results as participants already affected by respiratory symptoms at the time of this study may have changed jobs or changed their work environment to reduce their exposure to metals. Therefore, those participants would not be had been classified as metals exposure (104). Thus, by using, most recent or current job, the authors may have missed previous metals exposures, which may have influenced the overall null association found in this study. Another study from France, however, found that occupational exposure to metals was associated with reduced lung function in men and women (154). This study again limited by the use of most recent job to assess exposure and it is likely that the association observed in this study may have been affected by healthy worker effect.

Overall, findings from above mentioned studies are scant and inconsistent. Furthermore, very few studies were conducted, and none of the studies have used lifetime occupational history along with post-BD spirometry to assess this relationship, which is a major limitation in the current literature.

Table 2.16: Population-based studies investigating the association between metals exposure and COPD

First author (year)	Location	Sample size	Methods of exposure assessment	Duration of jobs	BD	Definitions used	Any exposure OR(95%CI)
Cross-sectional studies							
Dijkstra et al. (2014) (104)	The Netherlands	10,008	ALOHA plus JEM	Current job	Pre	$FEV_1/FVC<0.7$	H=0.92(0.33-2.56) L=1.06(0.50-2.25)
Le Moual et al. (1994) (154)	France	10,046	JEM	Current job	Pre	Lung function	Men: mean FEV_1 H=-0.03 L=-0.03
							Women: mean FEV_1 H=-0.01 L=+0.31

Definition of abbreviations: BD=Bronchodilator; CI= Confidence Interval; H=High Exposure; L=Low Exposure; JEM=Job Exposure Matrix; OR=Odds Ratio

2.7 Association between occupational exposures and lung function decline

There is limited evidence from population-based longitudinal studies that occupational exposures may be associated with accelerated decline in lung function (summarized in Table 2.17). Of the eight studies presented in Table 2.17, most of the studies examined a possible association with dust, gases, and fumes or combined exposure to VGDF using self-reported exposure data. Three studies used the ALOHA JEM to assign exposure (84, 90, 165). Of these, one study reported an association with biological dust, mineral dust, gases/fumes (84); one study reported an association with VGDF and pesticide exposure (90); and one study reported that *SERPINA1* PiMZ genotype, in combination with smoking, significantly modified the association between occupational exposure to VGDF and lung function change (165). No studies investigated the effect of solvents and metals exposure with lung function decline.

A study from the USA investigated occupational dust exposure and reported a significant association with accelerated decline in FEV_1 but not FEV_1/FVC (166). However, this study used a modified version of the COPD JEM and a questionnaire to assign exposure and participants were asked whether they were more likely or less likely to be exposed to dust. Another study from the Netherlands used the ALOHA plus JEM and reported a significant association between both high and low exposure to pesticide and accelerated decline in FEV_1 and FEV_1/VC (vital capacity) (90). This study also found an association between cumulative exposure to the pesticide and accelerated decline in FEV_1 and a significant association between combined exposures to VGDF and accelerated decline in FEV_1 (90). However, they used the current job to assign exposure (90), and due to the effect of survivor bias, lack of information of exposures in early working life may have been missed (92). Three studies found a significant association between self-reported exposure to dust, gases, and fumes exposure with lung function decline (167-169). In contrast, the multi-centre ECRHS study did not find a significant association between the ALOHA JEM based biological dust, mineral dust, and gases/fumes exposures and lung function decline (84). The null finding in this study may have been due to the relatively younger age of the study population (20 to 44 years) and relatively short follow-up time of the cohort. Furthermore,

this study was also limited by the use of current job and did not report the association with cumulative exposure.

In summary, the evidence from population-based longitudinal studies on the association between occupational exposures and lung function decline is limited and contradictory. Studies that found an association may be affected by the healthy worker effect due to the use of current job and self-reported exposure. Furthermore, most of the studies assessed this association with dust, gases, and fumes exposure, but to date, no longitudinal studies have been conducted with solvents and metals exposure. A limited number of population-based longitudinal studies also reported the cumulative duration of exposure, which is an important predictor to make a robust conclusion in this relationship.

Table 2.17: Longitudinal population-based studies investigating the association between occupational exposure and lung function decline

First author (year)	Location	Sample size	Duration of follow-up	Methods of exposure assessment	Duration of jobs	Exposure category	Measure of lung function decline	Main results	Cumulative exposure (years)
Liao et al. (2015) (166)	USA	1,332	17 years	Mini JEM	Longest job	More likely/less likely dust exposure	FEV_1 (mL), FEV_1/FVC ratio	Dust exposure was associated with the LF decline	N/A
de Jong et al. (2014) (90)	The Netherlands	2,527	25 years	ALOHA plus JEM	Current job	High/low exposure to VGDF and pesticide	FEV_1(mL/yr), FEV_1%VC	Pesticide was associated with LF decline	Association with VGDF and pesticide
Mehta et al. (2014) (165)	Switzerland	3,739	10 years	ALOHA JEM	Current job	VGDF exposure	FEV_1 (mL), FEV_1/FVC ratio	Association was modified by *SERPINA1* PiMZ genotype	Association present
Harber et al. (2007) (167)	USA and Canada	5,724	5 years	SR	Current job	Dust and fumes	FEV_1 (% predicted), FEV_1/FVC ratio	Fumes exposure was associated with LF decline	N/A
Sunyer et al. (2005) (84)	Multicenter (ECRHS)	8,263	8.9 years	ALOHA JEM	Current job	Biological dust, mineral dust, gases/fumes	FEV_1(mL/yr), FEV_1/FVC ratio	No association	N/A
Lindberg et al. (2005) (170)	Sweden	1,655	10 years	SR	NA	No category	FEV_1 (% predicted), FEV_1/FVC ratio	No association	10-year cumulative incidence was 13.5% for COPD
Humerfelt et al. (1993) (168)	Norway	951	20-25 years	SR	NA	Mineral dust, gases, vapor and fumes	FEV_1 (mL/yr)	Gases and fumes was associated with LF decline	N/A
Krzyzanowski et al. (1986) (169)	Poland	1,824	13 years	SR	Last 5 years	Dust and fumes	FEV_1 (mL/yr)	Men exposed to dust and chemicals were associated with LF decline	N/A

Definition of abbreviations: ECRHS=European Community Respiratory Health Survey; JEM=Job Exposure Matrix; N/A= Not Available; SR=Self-Reported; VC= Vital Capacity; USA=United States of America; VGDF=Vapor, Gases, Dust, Fumes

2.8 Influence of sex on occupational exposure and COPD

In the past decades, COPD as defined by fixed AO has been considered a disease that mainly affects men, reflecting the higher prevalence of smoking among men compared to women. However, growing evidence suggests that COPD affects the sexes differently and in some cases exclusively in women (171). The reasons for greater susceptibility of women to airflow obstruction are largely unknown (27), but may be related to occupational exposures in non-male dominated occupations, such as nursing, cleaning or farming; increased exposure to residential inhaled pollutants compared to men; or may be associated with hormonal differences (171, 172).

A recent study from New Zealand reported that women had higher occupational exposures compared to men as women are mostly involved in non-male dominated occupations that involve exposure to chemicals such as hair dyes, textile dust, household dust, and cleaning occupations (28). This study also reported that women were also involved in traditionally male dominated work such as painting, printing, handling chemicals, and they were more likely to perform repetitive tasks compared to men in the same occupation (28). A similar sex difference was observed in an Australian study, which found that jobs with exposure to biological dust was a significant contributor to the development of airflow obstruction in women compared to men (19). A study from the USA also investigated the effect of sex and found a higher prevalence of occupational exposure in women compared to men in several job categories including agriculture, textiles, rubber, and plastics industries (173). Another study from France demonstrated that the association between FEV_1 and self-reported exposure to dust, gases, and fumes was slightly higher in women than men (174). However, in the same study when exposure was classified using the JEM, again similar trends of association were observed in women. In contrast, some previous studies that assessed occupational exposure in men and women, did not find any difference between the groups (20, 84, 85).

In summary, these results provide evidence that occupational exposure may contribute to the development of COPD differently in women and men. Although there were some contradictory findings, the majority of studies did find a significant difference between

men and women. There is suggestive evidence that women may have slightly different susceptibility to the effects of biological dust exposure. These preliminary findings require further investigation to better understand and quantify the potential role of a range of occupational exposures in contributing to the growing prevalence of COPD among women.

2.9 Summary of knowledge gaps in the current literature

This literature review shows mounting evidence; that occupational exposures are associated with respiratory symptoms, chronic bronchitis, COPD, and lung function. However, some major gaps in our knowledge clearly indicate the need for further investigation of occupational exposures and their relationship with these outcomes to advance the current knowledge in this field of research.

The association between occupational exposures and COPD has been predominately examined in cross-sectional studies. Findings from these studies are mixed and share some limitations which include lack of use of lifetime work history calendars for exposure assessment; lack of cumulative exposure assessment; and use of pre-BD spirometry rather than post-BD spirometry to define fixed type of AO. Importantly there have been a limited number of longitudinal studies which are important for determining a causal role of occupational exposures in disease risk. Furthermore, some important exposures (for example pesticides, solvents, and metals) have only recently been identified as having a role in respiratory symptoms and COPD.

Most studies used different exposure assessment methods that make it difficult to draw robust conclusions. Studies using job titles and the ALOHA JEM found some associations but were still limited by the use of current or most recent job to assign the exposures rather than lifetime work history. It is likely that the use of current jobs may underestimate the true impact of occupational exposures, because participants affected by respiratory symptoms at the time of an earlier job may have changed their job to reduce their exposure. Thus, these participants would not be classified as exposed and the healthy worker effect may have biased the results. In a JEM-based exposure assessment, it is possible to assign exposures based on lifetime occupational history that also allows for the calculation

of cumulative duration of exposure. Cumulative exposure is important in chronic disease assessment as it indicates total duration of exposure and it can then be related to the outcome of interest. A major limitation of the literature to date is that no studies have reported cumulative exposure to pesticides, solvents or metals and their relationship with COPD, respiratory symptoms, and lung function decline.

Very few studies have used post-BD spirometry to define fixed AO and those who used post-BD spirometry have reported inconsistent results. This is a major limitation of the current literature exploring the association between occupational exposure and COPD. In addition, there are inconsistencies in the definition of airflow obstruction, some studies used GOLD, some studies used LLN, and some studies used both. There is controversy over which definition is best to define fixed AO. Both the GOLD and LLN criteria recommend the use of post-BD spirometry to distinguish reversible (asthma) from irreversible (COPD) obstruction, particularly in younger adults (42, 175). Previous studies also highlighted the importance of post-BD spirometry, because it is essential to establish a temporal relationship between occupational exposure and risk of COPD in the general population.

Longitudinal studies can provide the strongest evidence for an association between occupational exposures and COPD and lung function decline. Longitudinal studies minimize the possibility of recall and other biases found in case-control studies, and survivor bias found in cross-sectional studies. The use of JEMs, along with lifetime occupational histories, in population-based studies also allows more precise quantification of risk estimates, as shown by different studies (19, 103). Furthermore, the potential effect modification by sex on the relationship between occupational exposures and COPD and lung function decline, is not yet established. Nor is it understood whether the effect of sex on these exposures is multiplicative or just additive.

My doctoral work aims to address some of the major gaps in knowledge identified in this literature review, with a particular focus on specific exposure to biological dust, mineral dust, gases/fumes, pesticides, solvents, and metals on COPD, respiratory symptoms and lung function decline.

Chapter 3 Occupational exposure and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analysis

3.1 Chapter introduction

This chapter includes my published systematic review and meta-analyses investigating the association between occupational exposure and risk of COPD (54). This systematic review was set as an aim of my PhD project. As this chapter is more relevant to the current literature exploring the relationship between occupational exposure and airflow obstruction, it is included following the literature review of my thesis.

This publication is the first systematic review and meta-analysis investigating this association using an objective measurement of spirometry and uniform measure of occupational exposure using the ALOHA JEM.

I was the first author of this manuscript, and the abstract of this paper has been presented at the 2014 Thoracic Society of Australia and New Zealand (TSANZ) annual conference held at the Gold Coast in Queensland, Australia (176).

3.2 Research questions and aims

3.2.1 Research question

1. What is the relationship between occupational exposure to biological dust, mineral dust, and gases/fumes assessed by the ALOHA JEM and COPD and chronic bronchitis?

3.2.2 Research aims

1. To systematically synthesize and meta-analyse the association between occupational exposure to biological dust, mineral dust, and gases/fumes assessed by the ALOHA JEM and COPD.
2. To systematically synthesize and meta-analyse the association between occupational exposure to biological dust, mineral dust, and gases/fumes assessed by the ALOHA JEM and chronic bronchitis.

3.3 Publication

3.3.1 Main document

Alif S, Dharmage S, Bowatte G, Karahalios A, Benke G, Dennekamp M, Mehta A, Miedinger D, Künzli N, Hensch N, Matheson M. Occupational exposure and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analysis. *Expert Rev Respir Med*. 2016; 10: 861-872.

EXPERT REVIEW OF RESPIRATORY MEDICINE, 2016
VOL. 10, NO. 8, 861–872
http://dx.doi.org/10.1080/17476348.2016.1190274

Taylor & Francis
Taylor & Francis Group

REVIEW

Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis

Sheikh M. Alif[a], Shyamali C. Dharmage[a,b], Gayan Bowatte[a], Amalia Karahalios[c], Geza Benke[d], Martine Dennekamp[d], Amar J. Mehta[e], David Miedinger[f,h], Nino Künzli[g,h], Nicole Probst-Hensch[g,h] and Melanie C. Matheson[a,b]

[a]Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia; [b]Population Health, Murdoch Childrens Research Institute, Melbourne, VIC, Australia; [c]Biostatistics Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, VIC, Australia; [d]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia; [e]Department of Environmental Health, Harvard T.H.Chan School of Public Health, Harvard University, Boston, MA, USA; [f]Clinic of Internal Medicine, Kantonsspital Baselland, Liestal, Switzerland; [g]Department of Epidemiology and Public Health, Swiss Tropical and Public Health Institute, Basel, Switzerland; [h]Medical Faculty, University of Basel, Basel, Switzerland

ABSTRACT

Introduction: Due to contradictory literature we have performed a systematic review and meta-analyse of population-based studies that have used Job Exposure Matrices to assess occupational exposure and risk of Chronic Obstructive Pulmonary Disease (COPD).

Areas covered: Two researchers independently searched databases for published articles using pre-defined inclusion criteria. Study quality was assessed, and results pooled for COPD and chronic bronchitis for exposure to biological dust, mineral dust, and gases/fumes using a fixed and random effect model. Five studies met predetermined inclusion criteria. The meta-analysis showed low exposure to mineral dust, and high exposure to gases/fumes were associated with an increased risk of COPD. We also found significantly increased the risk of chronic bronchitis for low and high exposure to biological dust and mineral dust.

Expert commentary: The relationship between occupational exposure assessed by the JEM and the risk of COPD and chronic bronchitis shows significant association with occupational exposure. However, the heterogeneity of the meta-analyses suggests more wide population-based studies with older age groups and longitudinal phenotype assessment of COPD to clarify the role of occupational exposure to COPD risk.

ARTICLE HISTORY
Received 5 November 2015
Accepted 27 April 2016
Published online
30 June 2016

KEYWORDS
Occupational exposure; job exposure matrix; ALOHA JEM; chronic obstructive pulmonary disease; COPD

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic respiratory condition characterized by airflow limitation that is not fully reversible [1]. The irreversible component of airflow limitation is the end result of airway inflammation (resulting in chronic bronchitis) and parenchymal tissue destruction (resulting in emphysema) [2]. COPD is the fourth leading cause of death worldwide and mortality from COPD is expected to continue to rise as the worlds' population continues to age [3,4]. The major risk factor for COPD is exposure to tobacco smoke [5]. Tobacco smoking accounts for 54% of the COPD-related mortality for men aged between 30 and 69 years [5]. Despite the strong link between COPD and smoking, not all smokers develop COPD and not all people with COPD have been smokers [5]. Occupational exposure to dusts, gases, and fumes can also contribute to COPD independently of smoking [6]. Occupational exposure to irritant dusts, gases, and fumes when inhaled usually activate alveolar macrophages and leukocytes, causing release of reactive oxygen species that lead to inflammatory changes in the airways [7].

Several studies in different occupational groups such as farmers [8], bakers, and workers in the timber [9], cotton textile [10], manufacturing [11], and construction industries [12] had higher risk of COPD even after adjustment for important potential confounders such as cigarette smoking. Despite the clear links in industry-specific studies between occupational exposure and COPD, it is important to establish occupational exposure and COPD risk using population-based study [5]. In population-based studies, the source population is usually a general population, and they tend to work in a wide variety of jobs over their lifetime. A major advantage of population-based studies is that the problem of survivor bias and healthy worker effect is to some degree avoided [5,14]. Studies of the general population have reported inconsistent associations between COPD risk and occupational exposures, with some studies finding an association [15–18] while others reported no association [19–21]. These inconsistencies may be due to differences in the exposures measured (e.g. source and composition), the exposure assessment methods, the definitions of COPD, the study design, and the age of the study population [5,14,22].

CONTACT Melanie C. Matheson mcmat@unimelb.edu.au Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Level 3, 207 Bouverie St, Carlton 3053

© 2016 Informa UK Limited, trading as Taylor & Francis Group

Direct assessment of occupational exposure is difficult in population-based studies. Several different methods have been used including general questionnaires on job characteristics, self-reported exposure via questionnaires, expert evaluation by an occupational hygienist, and the application of a Job Exposure Matrix (JEM) to self-reported work histories [14,23]. A JEM is a systematic tool for assigning exposure based on the cross-classification of occupational titles with agents [13,24]. The first JEM was developed for carcinogen exposures in the 1980s [24]. Since this original JEM, several disease-specific JEMs have been developed including a JEM for COPD called the ALOHA JEM [21]. This JEM identified exposures to biological dust, mineral dust, and gases/fumes as relevant for COPD and classified the subjects into no exposure, low-exposure, and high-exposure categories [18]. JEMs are categorized into general population-based JEMs, agent-specific JEMs, disease-specific JEMs, and industry-specific JEMs [25]. Population-based JEMs cover all jobs or occupations of a general (nationwide) classification, whereas agent-specific JEMs may have a matrix restricted to job titles occurring within the industry, or even within one facility [26]. JEMs are a useful method of occupational exposure assessment because they allow the study of exposure in a population-based sample that will be less affected by the healthy worker effect or the survivor effect commonly seen in occupational cohorts [23,27]. A further advantage of JEMs is that they consistently assign exposures, irrespective of the disease status of an individual, ultimately reducing differential information bias [25].

Several reviews have been conducted to synthesize the evidence for the relationship between occupational exposure and COPD [22,28–31]. A recent meta-analysis [22] found that exposure to vapors, dust, gases, or fumes (VGDF) was associated with higher risk of COPD; however, they combined all definitions of COPD, which varied between physician's diagnosed and objectively measured definitions. Furthermore, they used 'any exposure' as their measure of occupational exposure to VGDF and combined several different exposure assessment tools including self-reported exposure, expert evaluation of exposure, and JEM. They also did not include two important large European studies [17,21]. Due to these limitations, we have undertaken a systematic review and meta-analysis with the specific objective of examining the association between occupational exposure and COPD, using only studies that have used the ALOHA JEM to assess occupational exposure. We have also restricted our review to studies that have used objective definitions of COPD.

2. Materials and methods

We performed a systematic review and a meta-analysis of published population-based studies according to MOOSE [32] guideline.

2.1. Search strategy and terms

PubMed, Medline (Web of Science), Embase, and Scopus were searched for English-language peer-reviewed publications from January 1970 to April 2015 by combining two sets of keywords. One set of keywords included terms related to exposures, and another set included terms related to outcome(s). The following two sets of Medical Subject Headings (MeSH) and text words were used to identify publications.

(1) 'COPD' (MeSH) OR 'COAD' (MeSH) OR 'Chronic Obstructive Airway Disease' (MeSH) OR 'Chronic Obstructive Pulmonary Disease' (MeSH) OR 'Pulmonary Disease' (MeSH) OR 'Chronic Obstructive' (MeSH) OR 'Airway obstruction' (MeSH).
And
(2) 'JEM' (text word) OR 'Job Exposure Matrix' (text word) OR 'Job Exposure Matrices' (text word) OR 'ALOHA JEM' (text word) OR 'ALOHA Job Exposure Matrix' (text word) OR 'ALOHA Job Exposure Matrices' (text word) OR 'Occupational exposures' (MeSH).

2.2. Selection criteria

We included only population-based studies that examined the association between occupational exposures assessed by the ALOHA JEM and risk of COPD defined using lung function measurements. The exposures were biological dust, mineral dust, and gases/fumes and exposures were further subdivided into no-, low-, and high-exposure group. The primary outcome was COPD while chronic bronchitis was considered as a secondary outcome.

2.3. Definitions

Studies were included if they defined COPD using lung function measurements. In all studies, COPD was defined according to either: (1) a forced expiratory volume in 1 s over forced vital capacity [FEV_1/FVC] ratio less than 70% or (2) the lower limit of normal (LLN) criterion, defined as FEV_1/FVC ratio less than the fifth percentile. The LLN is calculated by the predicted value minus 1.645 the standard deviation of the predicted value [33]. We considered pre-bronchodilator spirometric values to define COPD in both definitions because only one of our included study [19] used post-bronchodilator spirometry.

Chronic bronchitis was defined as a self-reported cough or phlegm for at least 3 months during two consecutive years [6].

2.4. Relevant studies

Using predefined selection criteria, the eligibility of the studies generated by the search strategy were evaluated by two researchers. Occupational exposures, definitions of COPD, adjustment for possible confounders, and presented effect estimate with 95% confidence intervals (CI) were considered when pooling the data.

2.5. Data extraction and quality assessment of included studies

Study characteristics described in Table 1 were extracted from each article along with adjusted odds ratios (OR) and 95% CI. The quality of the included studies was assessed using the

Table 1. Characteristics of the included studies that examined the association between occupational exposures and COPD.

First author (year)	Study type	Location	Sample size	Age (years)	Occupational exposures	Method of assessment	COPD definition	BD	Chronic bronchitis definition	Adjustment for confounders	Adjustment for asthma	Statistical methods
Hansell et al. (2014)	Cross-sectional	New Zealand	1017	25–74	Biological dust, mineral dust, gases/fumes	Self-reported lifetime work history calendar	$FEV_1/FVC < 70\%$ $FEV_1/FVC < LLN$	Post	Cough and sputum >3 months	Age, sex, age squared, smoking (pack-years), ethnicity, and deprivation	Performed sensitivity analysis excluding asthmatics with unclear results due to small remaining numbers (sensitivity analysis results not presented in manuscript)	Multiple logistic regression
de Jong et al. (2014)	Cross-sectional	The Netherlands	1754	18–89	Biological dust, mineral dust, gases/fumes	Self-reported current job title	$FEV_1/FVC < 70\%$	Pre	Did not measure	Age, sex, height, weight, smoking status, pack-year smoked	Did not exclude asthmatics or adjust for asthma in analysis	Multiple logistic regression
Matheson et al. (2005)	Cross-sectional	Australia	1213	45–70	Biological dust, mineral dust, gases/fumes	Self-reported lifetime work history calendar	$FEV_1/FVC < 70\%$ $FEV_1/FVC < LLN$	Pre	Cough and phlegm >3 months	Age, sex, smoking status, pack-year smoked	Sensitivity analysis by excluding asthmatic, no change to estimates so full data set estimates presented	Multiple logistic regression
Sunyer et al. (1998)	Cross-sectional	Spain	1735	20–44	Biological dust, mineral dust, gases/fumes	Self-reported current job title at baseline	$FEV_1/FVC < 70\%$	Pre	Cough > 3 months +Phlegm > 3 months	Age, sex, smoking, area, and height	Excluded people with symptoms of asthma	Multiple logistic regression
Mehta et al. (2012)	Cohort	Switzerland	4267	18–62	Biological dust, mineral dust, gases/fumes	Self-reported current job title at baseline	$FEV_1/FVC < 70\%$ $FEV_1/FVC < LLN$	Pre	Did not measure	Age, sex, body mass index, respiratory infection at an early age, parental asthma, smoking status, pack-year smoked, environmental tobacco smoke, education, and area	Excluded people with asthma	Multiple logistic regression

BD: Bronchodilator; COPD: chronic obstructive pulmonary disease; LLN: lower limit of normal; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity.

Newcastle–Ottawa Quality Assessment Scale [34] for cohort and cross-sectional studies [35,36] (Table 2). Authors of two of the selected published articles [17,18] were contacted for further data analysis so that all estimates were comparable.

2.6. Statistical analysis

All studies reported OR and 95% CI for the low and high exposure to biological dust, mineral dust, and gases/fumes. Studies with similar type of exposures and uniform pattern of outcome assessment were combined for meta-analysis. The first phase of meta-analyses included studies that investigated low- and high-exposure to biological dust, mineral dust, gases/fumes, and risk of COPD, and the second phase of meta-analysis investigated low and high exposure to biological dust, mineral dust, gases/fumes, and risk of chronic bronchitis. Separate meta-analysis was conducted for $FEV_1/FVC < 70\%$ and $FEV_1/FVC < LLN$. The extracted estimates were stratified according to low- and high- exposure to biological dust, mineral dust, and gases/fumes. Heterogeneity between studies was assessed using Higgins I^2 statistic [37]. Fixed and random-effect meta-analyses were performed as the heterogeneity between studies varied. Publication bias of included studies was assessed by Egger's test [38] and funnel plot (data not shown) [39]. Stata 13.1 (Stata Corporation, College Station, Texas, USA) was used for the statistical analyses.

3. Results

3.1. Study selection

A total of 972 studies were identified after removing duplicates. Of these, 909 studies were eliminated after reading the abstracts and applying inclusion criteria, leaving 63 articles for full-text review. Among these 63 articles, only 5 studies met the inclusion criteria, 1 cohort [17] and 4 cross-sectional studies (Figure 1) [16,18,19,21]. Details of the reasons for exclusion are presented in Figure 1.

3.2. Study characteristics

Table 1 lists the features of the included studies. All five studies were conducted in Western countries. Of the included studies, four reported outcome data as prevalence [16,18,19,21] while one reported outcome data as incidence [17]. The sample sizes ranged from 1017 to 4267. The age at which the outcome of COPD was measured ranged from 18 to 89 years. Exposure assessment was performed using self-reported lifetime work history calendar [18,19], or self-reported current job title [16,17,21] at baseline and the ALOHA JEM.

3.3. Outcome measures

All studies used either the $FEV_1/FVC < 70\%$ or $FEV_1/FVC < LLN$, and three studies reported results using both definitions. The studies used different prediction equations, utilizing either the Quanjer prediction reference equation for 'Caucasians' derived from the European Coal and Steel Community reference population [40–42], or the third National Health and Nutrition Examination Survey (NHANES-III) study population [43]. Only one study reported the outcome using diagnosis made by post-bronchodilator spirometric measurement of FEV_1/FVC [19], all other studies used the pre-bronchodilator spirometry.

3.4. Occupational exposure and risk of COPD

3.4.1. Biological dust exposure

Figure 2 presents the associations from the studies that have examined the relationship between biological dust exposure and COPD, stratified by high or low biological dust exposure. Overall, there was little evidence of heterogeneity between the studies included in the meta-analysis, so fixed effects estimates are reported (see forest plots for I^2 values). For the studies that defined COPD by $FEV_1/FVC < 70\%$, there was no evidence of an increased risk of COPD associated with low biological dust exposure (OR = 1.06, 95% CI 0.96–1.17) or high biological dust exposure (OR = 0.98, 95% CI 0.79–1.21). The combined estimate for low or high biological dust exposure was also not associated with COPD (OR = 1.04, 95% CI 0.95–1.14, I^2 = 19.1%) (Figure 2).

For studies that used the $FEV_1/FVC < LLN$ definition of COPD, there was no increased risk of COPD associated with low (OR = 1.18, 95%CI 0.95–1.48) or high biological dust exposure. The combination of low or high biological dust exposure was also not associated with an increased risk of COPD using the $FEV_1/FVC < LLN$ definition (Figure 2).

3.4.2. Mineral dust exposure

The pooled estimates from the studies that examined the association between mineral dust exposure and COPD risk are presented in Figure 3. Studies that defined COPD by $FEV_1/FVC < 70\%$ showed a significantly increased risk of COPD for low exposure to mineral dust (OR = 1.17, 95% CI 1.04–1.31), but not for high exposure. The combined effect estimate for low or high mineral dust exposure was statistically significant (OR = 1.15, 95% CI 1.04–1.27). We did not observe any significant association between mineral dust exposure and COPD risk defined by $FEV_1/FVC < LLN$ (Figure 3).

3.4.3. Gases/fumes exposure

The meta-analysis for the association between gases/fumes exposure and COPD is presented in Figure 4. For studies that defined COPD by $FEV_1/FVC < 70\%$, there was no association between low exposure to gases/fumes (OR = 1.07, 95% CI 0.98–1.18) and COPD. For high exposure to gases/fumes, there was significant heterogeneity between studies (I^2 = 59.4%, P = 0.04) and no association with COPD for the random-effect estimate (OR = 1.03, 95% CI 0.73–1.45). The combined estimate for low or high gases/fumes exposure was statistically not significant (random effect OR = 1.08, 95% CI 0.95, 1.23, Figure 4). We also did not observe any significant association between low or high exposure to gases/fumes and risk of COPD defined by $FEV_1/FVC < LLN$ (Figure 4).

Table 2. Methodological quality score of included studies based on Newcastle–Ottawa Quality Assessment Score.

First author (year)	Selection				Comparability	Outcome			Total score
Cross-sectional studies	Representative of the exposed group	Selection of never exposed group	Ascertainment of exposure		Based on design and statistical analysis	Assessment of outcome	Sufficiently long exposure for outcomes		
Hansell et al. (2014)	1	1	0		1	1	1		5/7
de Jong et al. (2014)	1	1	0		1	1	1		5/7
Matheson et al. (2005)	1	1	0		1	1	1		5/7
Sunyer et al. (1998)	1	1	0		1	1	1		5/7
Cohort studies	Representative of the exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Based on design and statistical analysis	Assessment of outcome	Long enough follow-up	Adequacy of follow-up of cohorts	
Mehta et al. (2012)	1	1	0	1	2	1	1	1	8/9

3.5. Occupational exposure and risk of chronic bronchitis

Three of our included studies assessed the association between occupational exposure measured by the ALOHA JEM and risk of chronic bronchitis. Two studies [18,19] defined chronic bronchitis as a self-reported cough and phlegm for 3 months during 2 consecutive years, and one study [21] defined as either a self-reported cough or phlegm for 3 months during 2 consecutive years.

The meta-analysis showed a significantly increased risk of chronic bronchitis separately for low and high exposure to biological dust and mineral dust. Overall estimates for low and high biological dust and mineral dust exposure were also significant (Figure 5). There was no significant association between gases/fumes exposure and risk of chronic bronchitis in fixed or random-effect methods.

4. Discussion

This is the first systematic review and meta-analysis to investigate the association between occupational exposure and risk of COPD in population-based studies using robust measurement of both outcome and exposure. Five studies used the lung function to define COPD and the ALOHA JEM to assign exposure. Our meta-analysis of the three exposure categories of biological dust, mineral dust, and gases/fumes found that exposure to mineral dust and gases/fumes was associated with an increased risk of COPD defined by $FEV_1/FVC < 70\%$; while for COPD defined by $FEV_1/FVC < LLN$, there was no statistical significant association with biological dust exposure. Furthermore, we also found that chronic bronchitis symptoms were significantly associated with exposure to biological and mineral dust and a borderline association with gases/fumes.

Our findings support existing literature suggesting that occupational exposure is a significant contributor to risk of COPD. A recent review and meta-analysis found that any VGDF exposure was associated with an increased risk of COPD [22]. They included studies with all different methods of exposure assessment (expert assessment, self-report, and JEMs) and combined several different definitions of COPD ($FEV_1/FVC < 70\%$, $FEV_1/FVC < LLN$, self-reported symptoms, and doctors diagnosis). Age and study type were found to significantly affect the heterogeneity in the review by Ryu et al. [22], specifically finding that studies with participants less than 40 years did not show any association and case-control study designs showing the greater risk of COPD. We elected to have strict inclusion criteria for our exposure and outcome definitions and, therefore, had very little heterogeneity in our study estimates. We also observed smaller effect sizes than those found by Ryu et al. [22], possible due to the population-based study design inclusion criteria and because we examined the independent effects of biological dust, mineral dust, and gases/fumes exposure rather than combining all exposures together.

One of the main strengths of this review is the inclusion of population-based studies with objective measurement of lung function and a uniform measure of occupational exposure. We restricted our analysis to COPD based on spirometric criteria,

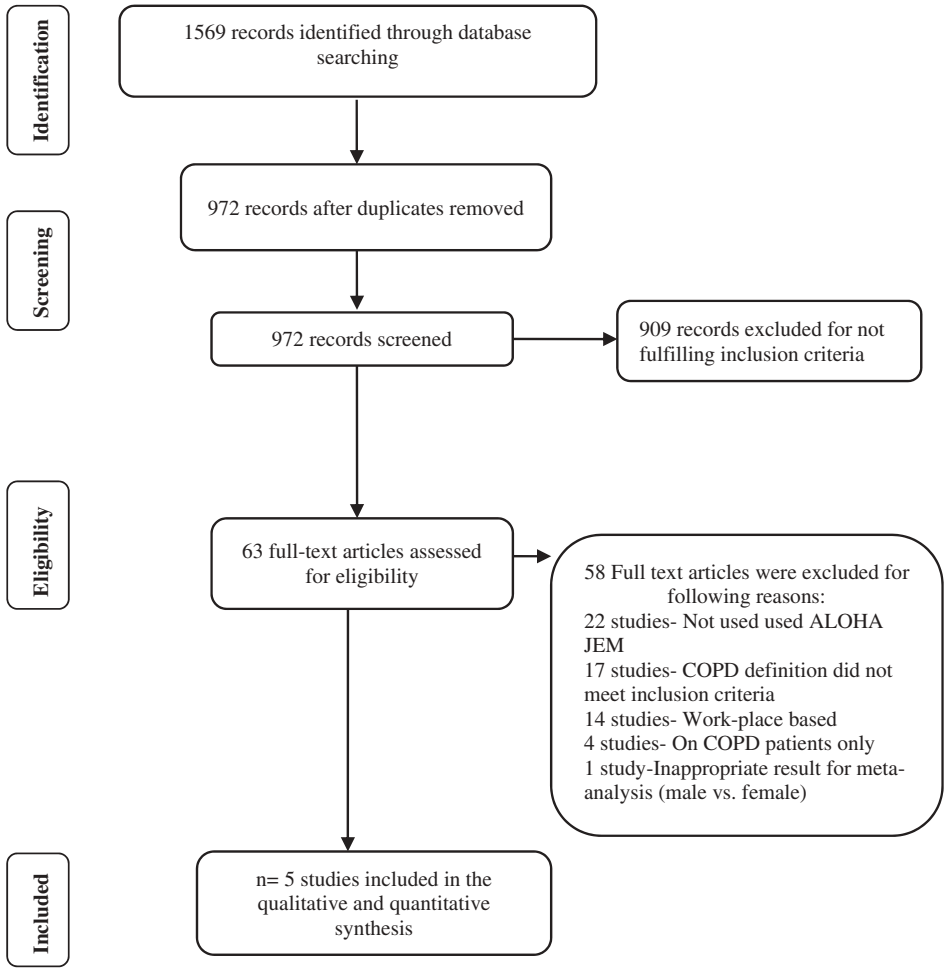


Figure 1. Diagrammatic presentation of study selection process.

but we were unable to define COPD based on post-bronchodilator measurements as only one study used post-bronchodilator spirometry [19]. This is a major limitation of the current literature exploring the relationship between occupational exposure and COPD. Post-bronchodilator spirometry is crucial to distinguish reversible (asthma) from irreversible (COPD) obstruction, particularly in younger adults [4,44]. Of the five studies included in this meta-analysis, two excluded participants with asthma [17,21] and two performed sensitivity analysis excluding asthmatics. Of the two studies that performed sensitivity analysis, one found no difference to the findings when excluding asthmatics [18] and the other found that they lost too many subjects for a reliable analysis but this was the one study that used post-bronchodilator spirometry [19]. Only one study in our review did not appear to make any adjustment for asthmatic subjects [16].

There is still debate over the best definition for COPD. Spirometry is the gold standard diagnostic procedure to define COPD but the degree of obstruction that establishes a diagnosis is still a matter of debate [45]. The Global Initiative for Obstructive Lung Disease (GOLD) defined COPD as a FEV_1/FVC ratio less than 70% [6] which has been widely utilized because of its practical application in clinical practice and in large-scale population-based studies. More recently, LLN has been recommended as better way to diagnosis COPD due to the more rapid decrease in FEV_1 than FVC with aging, causing over-diagnosis of COPD in older age groups [46]. Only three of our included studies [17–19] used both FEV_1/FVC < 70% and FEV_1/FVC < LLN to define COPD. Our meta-analyses using the two different definitions did produce different results with the FEV_1/FVC < LLN definition finding no significant association with biological dust, mineral dust or gases, and fumes exposure. The reason for this discrepancy is most likely due to reduced power in LLN analysis due to fewer cases of COPD.

Along with COPD defined by spirometry, we also explored the association between occupational exposure and chronic bronchitis defined by a productive cough and sputum. We found that biological and mineral dust exposures are both associated with increased risk of chronic bronchitis. Several other studies that have used other methods of occupational exposure assessment, such as self-reported exposure, have also shown an increased risk of chronic bronchitis due to dust exposure [47–51]. Population-based studies have also shown that certain occupation groups with known biological dust exposure such as farmers [52] and food industry workers [50] have a greater risk of chronic bronchitis.

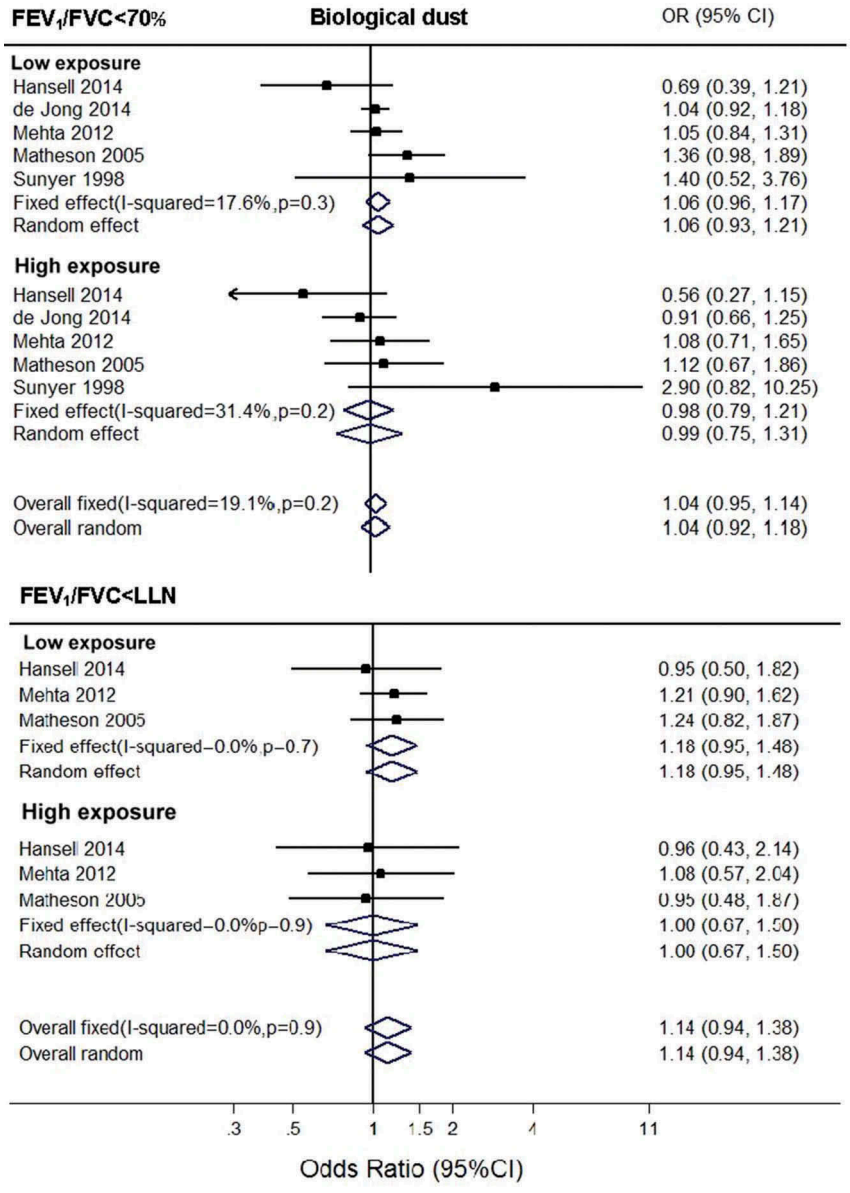


Figure 2. Association between biological dust exposure and COPD.

Strengths of our review include the strict inclusion and exclusion criteria. The use of the ALOHA JEM to define occupational exposure enabled us to examine the effects of the three exposure categories separately. JEMs are also less affected by recall bias and differential misclassification of exposure when compared with self-reported exposure [53]. The strength of our study is the use of spirometrically defined COPD, which is the gold-standard for the definition of COPD. However, the small number of studies meeting these criteria created some limitations including reduced statistical power for the pooled estimate and inability to assess quantitative estimates of publication bias. We assessed publication bias by visual inspection of funnel plots and did not observe any clear trends of bias (data not shown). We were also unable to perform any subgroup analysis because the studies did not consistently provide results stratified by factors of interest (e.g. age and sex). All except one of the study [17] included in this review did not differentiate between the stages of COPD; this is due to the young age of participants in most of the studies and, therefore, the lack of sufficient cases with more severe COPD.

In summary, we observed an increased risk of COPD associated with exposure to low levels of mineral dust and high levels of gases/fumes. The lack of association with high exposure is likely due to the relatively younger age of study subjects in most cohorts. Along with the associations with COPD, we also demonstrated that chronic bronchitis is associated with low and high exposure to biological and mineral dust. This is an important study with significant implications for public health as we have confirmed with a rigorous review with strict inclusion criteria that occupational exposure plays a significant role in COPD in the general population, not just people in high-risk occupations. Our review strengthens and highlights the need for

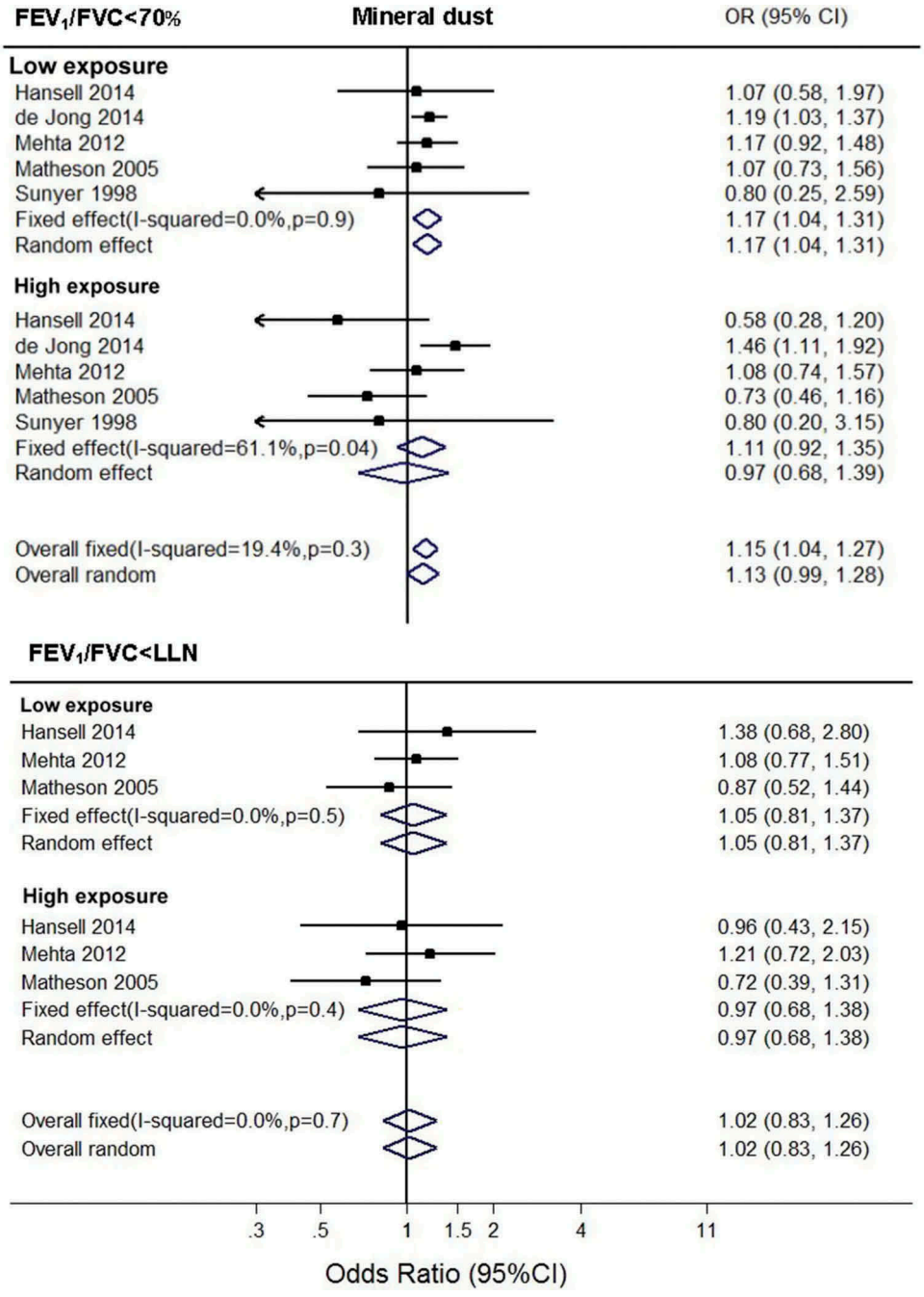


Figure 3. Association between mineral dust exposure and COPD.

strict ventilation and personal protective equipment policies in relation to occupations with even low-level exposure.

5. Expert commentary

Traditionally, in epidemiological research of COPD, post-bronchodilator FEV_1/FVC ratio has been used to define cases using either the GOLD criteria or the LLN cutoff value. These definitions do not take into account any symptoms; the individual may be experiencing. Utilizing these objective measurement thresholds is important for population-based studies allowing greater consistency and providing better comparability of results across studies, but it fails to take into account the individual variability of symptoms. Individuals with the same FEV_1/FVC measurement may experience vastly different impacts on their daily functioning and quality of life. Future research into COPD and occupational exposure would benefit from additional clinical objective measurements such as X-rays, CT scans, or other lung function measurements. This will enable to disease process in relation to occupational exposure to be characterized more accurately.

In population-based studies, JEMs are useful tools to quantify in a large number of individuals' occupational exposure in a systematic objective manner. However, JEMs have their limitations and improvements such as the inclusion of more specific agents, a quantitative measurement of exposure, time

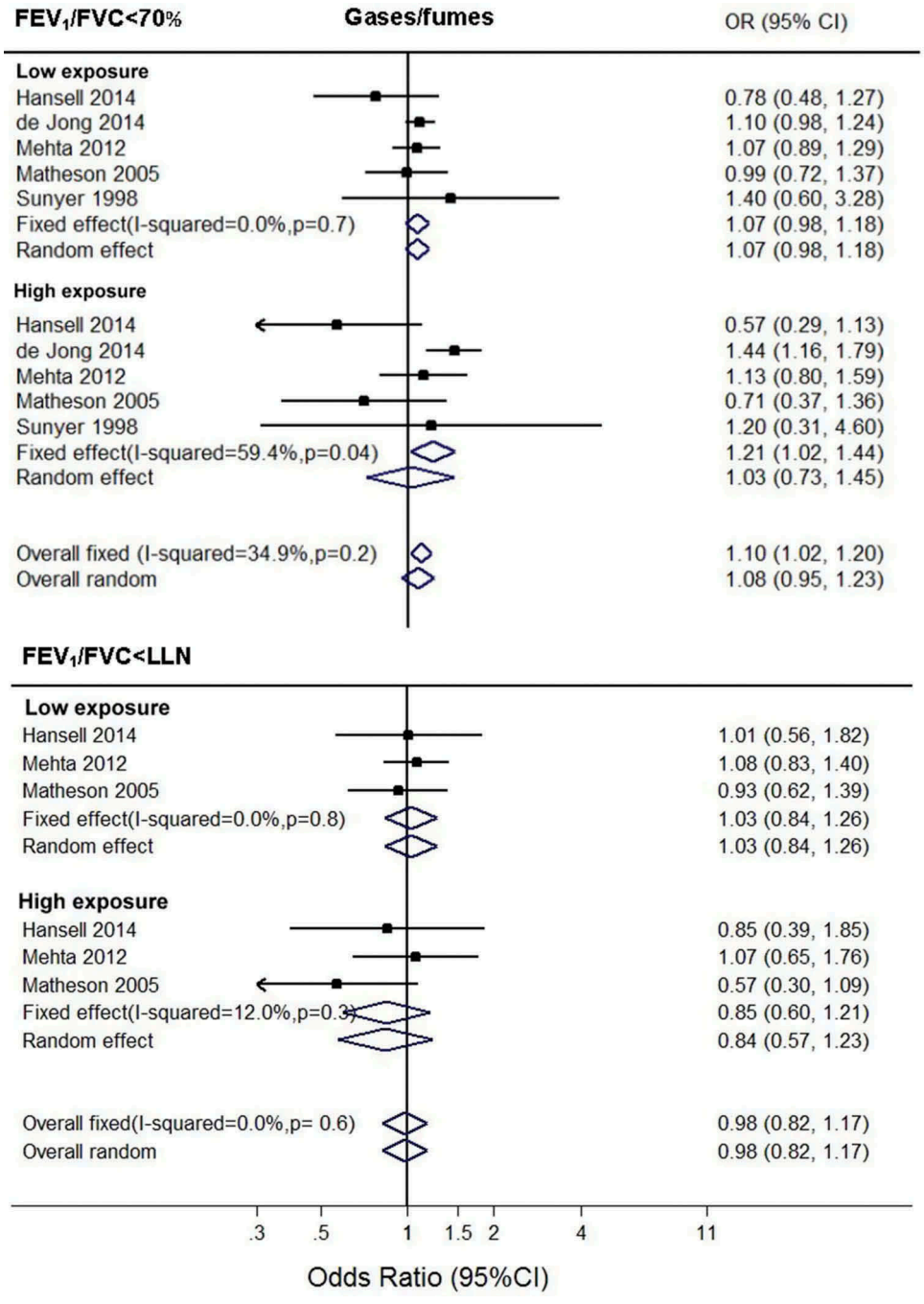


Figure 4. Association between gases/fumes exposure and COPD.

periods with variable quantitative exposure assessment, and country specification would all improve their utility.

There is an emerging trend of combining large multi-cohort data set to increase sample size and obtain greater statistical power for all types of studies including investigation of occupational exposure and respiratory diseases. Combining multiple cohorts has limitations, but importantly, it does enable greater power to examine important research questions that are nearly impossible in smaller individual cohorts such as studies of COPD incidence, COPD persistence, more severe COPD, and decline in lung function. While much research is needed to advance our knowledge in this field, there is sufficient evidence thus far on the link between occupational exposures and COPD that warrants educating the general public and implementing safe practices at the work place.

6. Five-year view

Population-based studies enable the risk in the broader community to be assessed, and tools such as the ALOHA are vital in estimating exposure in large-scale population studies. Future studies would benefit from further development of

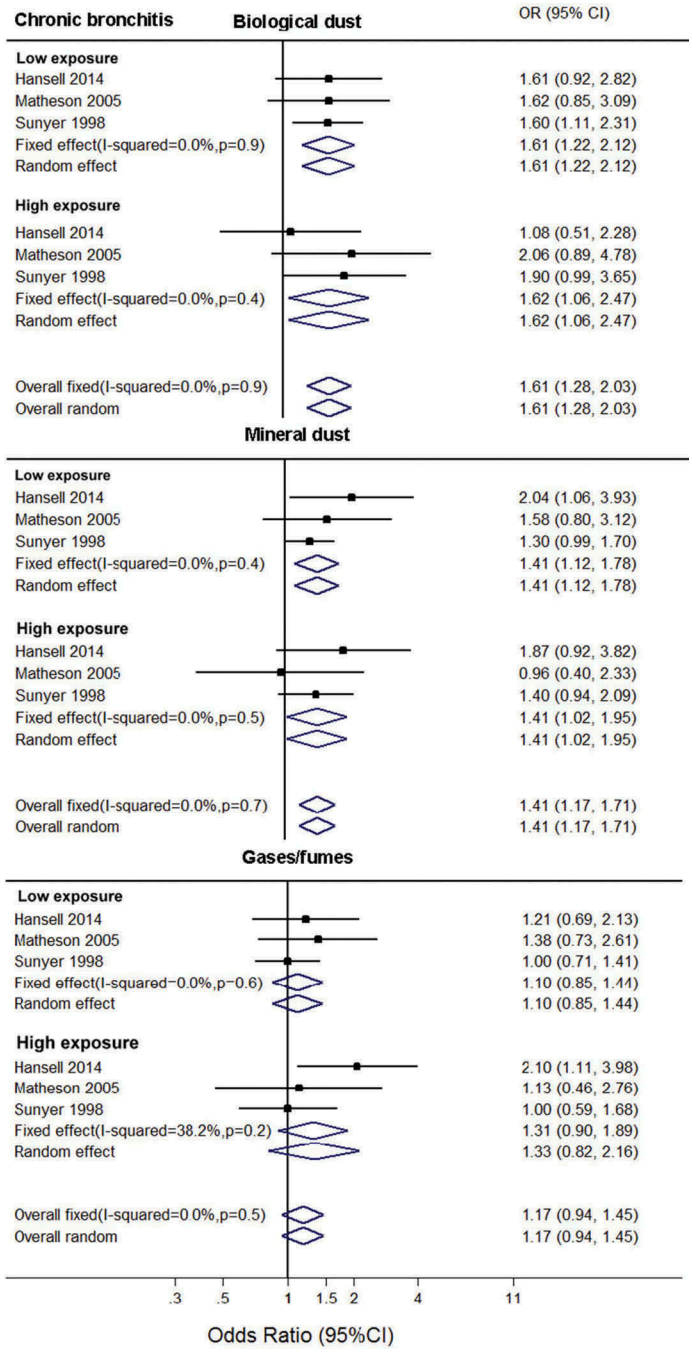


Figure 5. Association between biological dust, mineral dust and gases/fumes exposure and chronic bronchitis.

occupational assessment tools including further refinement of exposure to give a more quantitative estimates like that in for example FINJEM (Finnish Job Exposure Matrix). Long-term follow-up of population-based cohorts including repeated spirometry assessments to objectively define COPD incidence and assess lung function are needed.

Key issues

- Post-bronchodilator spirometry definition of COPD is essential to establish a temporal relationship between occupational exposure and risk of COPD and subtypes in the general population.
- It is important to assess the occupational contribution of COPD in the early middle age adult population using lifetime work history calendar in a longitudinal study, to date, very few literature summarize this evidence.
- Despite the inconsistency between definitions, study design, the inclusion of young adult in the literature, this meta-analysis found that occupational exposure may increase the risk of COPD and chronic bronchitis in the general population.
- However, there was also conflicting evidence whether sex and smoking modified the association or confounded by the previous history of asthma or socioeconomic status that usually influences people's job choice.

Declaration of interest

SM Alif is supported by a Melbourne International Research Scholarship. G Bowatte is supported by a university of Melbourne Scholarship and a National Health and Medical Research Council (NHMRC) of Australia Centre for Air Quality and Health Research and Evaluation (CAR) scholarship. SC Dharmage and MC Matheson are supported by the NHMRC. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–946.
2. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Resp Crit Care Med. 2013;187(4):347–365.
3. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015;385 (9971):899–909.
4. Abramson MJ, Perret JL, Dharmage SC, et al. Distinguishing adult-onset asthma from COPD: a review and a new approach. Int J Chron Obstruct Pulmon Dis. 2014;9:945–962.
5. Eisner MD, Anthonisen N, Coultas D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Resp Crit Care Med. 2010;182(5):693–718.
6. Pauwels RA, Buist AS, Calverley PMA, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. Am J Resp Crit Care Med. 2001;163(5):1256–1276.
7. Doelman CJ, Leurs R, Oosterom WC, et al. Mineral dust exposure and free radical-mediated lung damage. Exp Lung Res. 1990;16 (1):41–55.
8. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. Chest. 2009;136 (3):716–725.
9. Mandryk J, Alwis KU, Hocking AD. Work-related symptoms and dose-response relationships for personal exposures and pulmonary function among woodworkers. Am J Ind Med. 1999;35 (5):481–490.
10. Christiani DC, Wang X-R, Pan L-D, et al. Longitudinal changes in pulmonary function and respiratory symptoms in cotton textile workers: a 15-yr follow-up study. Am J Resp Crit Care Med. 2001;163(4):847–853.
11. Nordby KC, Fell AK, Noto H, et al. Exposure to thoracic dust, airway symptoms and lung function in cement production workers. Eur Respir J. 2011;38(6):1278–1286.
12. Torén K, Järvholm B. Effect of occupational exposure to vapors, gases, dusts, and fumes on COPD mortality risk among Swedish construction workers: a longitudinal cohort study. Chest. 2014;145 (5):992–997.
13. McGuire V, Nelson LM, Koepsell TD, et al. Assessment of occupational exposures in community-based case-control studies. Annu Rev Public Health. 1998;19:35–53.
14. Balmes J, Becklake M, Blanc P, et al. American Thoracic Society statement: occupational contribution to the burden of airway disease. Am J Resp Crit Care Med. 2003;167(5):787–797.
15. Würtz ET, Schlünssen V, Malling TH, et al. Occupational chronic obstructive pulmonary disease in a Danish population-based study. COPD J Chronic Obstructive Pulm Dis. 2014;12(4):435–443.
16. de Jong K, Boezen H, Kromhout H, et al. Pesticides and other occupational exposures are associated with airway obstruction: the lifelines cohort study. Occup Environ Med. 2014;71(2):88–96.
    • **Conducts a comprehensive comparison of occupational exposure and COPD in two different cohort using different definitions of COPD.**
17. Mehta AJ, Miedinger D, Keidel D, et al. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary diseases in the Swiss cohort study on air pollution and lung and heart diseases in adults. Am J Resp Crit Care Med. 2012;185(12):1292–1300.
    • **Conducts occupational exposure assessment and risk of COPD defined by pre-bronchodilator spirometry in SAPALDIA cohort.**
18. Matheson MC, Benke G, Raven J, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax. 2005;60(8):645–651.
    • **Conducts occupational exposure assessment in early middle-aged adult Australian population.**
19. Hansell A, Ghosh RE, Poole S, et al. Occupational risk factors for chronic respiratory disease in a New Zealand population using lifetime occupational history. J Occup Environ Med. 2014;56(3):270–280.
    • **Only study that defines COPD using post-bronchodilator spirometry.**
20. Sunyer J, Zock JP, Kromhout H, et al. Lung function decline, chronic bronchitis, and occupational exposures in young adults. Am J Resp Crit Care Med. 2005;172(9):1139–1145.
    •• **ECRHS study conducted in young adult but did not meet the inclusion criteria of this meta-analysis.**
21. Sunyer J, Kogevinas M, Kromhout H, et al. Pulmonary ventilatory defects and occupational exposures in a population-based study in Spain. Am J Resp Crit Care Med. 1998;157(2):512–517.
    • **ECRHS study conducted in young adult.**
22. Ryu JY, Sunwoo YE, Lee SY, et al. Chronic obstructive pulmonary disease (COPD) and vapors, gases, dusts, or fumes (VGDF): a meta-analysis. COPD J Chronic Obstructive Pulm Dis. 2014;12(4):374–380.
23. Tielemans E, Heederik D, Burdorf A, et al. Assessment of occupational exposures in a general population: comparison of different methods. Occup Environ Med. 1999;56(3):145–151.
24. Hoar SK, Morrison AS, Cole P, et al. An occupation and exposure linkage system for the study of occupational carcinogenesis. J Occup Med. 1980;22(11):722–726.
25. Kauppinen TP, Toikkanen J, Pukkala E. From cross-tabulations to multipurpose exposure information systems: a new job-exposure matrix. Am J Ind Med. 1998;33(4):409–417.
26. Kauppinen TP. Assessment of exposure in occupational epidemiology. Scand J Work Environ Health. 1994;20(Spec No):19–29.
27. Le Moual N, Bakke P, Orolowski E, et al. Performance of Population specific job exposure matrices (JEMs): European collaborative analysis on occupational risk factors for chronic obstructive pulmonary disease with job exposure matrices (ECOJEM). Occup Environ Med. 2000;57(2):126–132.
28. Omland Ø, Würtz ET, Aasen TB, et al. Occupational chronic obstructive pulmonary disease: a systematic literature review. Scand J Work Environ Health. 2014;40(1):19–35.
29. Brüske I, Thiering E, Heinrich J, et al. Biopersistent granular dust and chronic obstructive pulmonary disease: a systematic review and meta- analysis. PLoS One. 2013;8(11):1–10.
30. Cullinan P. Occupation and chronic obstructive pulmonary disease (COPD). Br Med Bull. 2012;104:143–161.
31. Dutkiewicz J, Jabionski L, Olenchock SA. Occupational biohazards: a review. Am J Ind Med. 1988;14(5):605–623.
32. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA. 2000;283(15):2008–2012.

33. Cerveri I, Corsico A, Accordini S, et al. Underestimation of airflow obstruction among young adults using FEV1/FVC,70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. Thorax. 2008;63(12):1040–1045.
34. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603–605.
35. Herzog R, Álvarez-Pasquin MJ, Díaz C, et al. Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. BMC Public Health. 2013;13(1):1–17.
36. Suvan J, D'Aiuto F, Moles DR, et al. Association between overweight/obesity and periodontitis in adults. A systematic review. Obes Rev. 2011;12(5):381–404.
37. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560.
38. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315 (7109):629–634.
39. Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. J Clin Epidemiol. 2000;53(11):1119–1129.
40. Baur X, Isringhausen-Bley S, Degens P. Comparison of lung-function reference values. Int Arch Occup Environ Health. 1999;72 (2):69–83.
41. Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(16):5–40.
42. Quanjer PH, Dalhuijsen A, Van Zomeren B. Summary equations of reference values. Bull Eur Physiopathol Respir. 1983;19(5):45–51.
43. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Resp Crit Care Med. 1999;159(1):179–187.
44. Sterk P. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV_1. Eur Respir J. 2004;23(4):497–498.
45. Swanney MP, Ruppel G, Enright PL, et al. Using the lower limit of normal for the FEV_1/FVC ratio reduces the misclassification of airway obstruction. Thorax. 2008;63(12):1046–1051.
46. Hardie J, Buist A, Vollmer W, et al. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J. 2002;20(5):1117–1122.
47. Marchetti N, Garshick E, Kinney GL, et al. Association between occupational exposure and lung function, respiratory symptoms, and high-resolution computed tomography imaging in COPDGene. Am J Resp Crit Care Med. 2014;190(7):756–762.
48. Rodrıguez E, Ferrer J, Zock JP, et al. Lifetime occupational exposure to dusts, gases and fumes is associated with bronchitis symptoms and higher diffusion capacity in COPD patients. PLoS One. 2014;9 (2):1–7.
49. Zock JP, Sunyer J, Kogevinas M, et al. Occupation, chronic bronchitis, and lung function in young adults an international study. Am J Resp Crit Care Med. 2001;163(7):1572–1577.
•• **ECRHS study that assessed the occupational contribution to the risk of chronic bronchitis and lung function but did not meet the inclusion criteria of this meta-analysis.**
50. Fishwick D, Bradshaw LM, D'Souza W, et al. Chronic bronchitis, shortness of breath, and airway obstruction by occupation in New Zealand. Am J Resp Crit Care Med. 1997;156(5):1440–1446.
51. Medina-Ramón M, Zock JP, Kogevinas M, et al. Asthma, chronic bronchitis, and exposure to irritant agents in occupational domestic cleaning: a nested case-control study. Occup Environ Med. 2005;62(9):598–606.
52. Melbostad E, Eduard W, Magnus P. Chronic bronchitis in farmers. Scand J Work Environ Health. 1997;23(4):271–280.
53. Mannetje A, Kromhout H. The use of occupation and industry classifications in general population studies. Int J Epidemiol. 2003;32(3):419–428.

Chapter 4 Methods

The research findings presented in this thesis is based on the Tasmanian Longitudinal Health Study (TAHS), previously known as Tasmanian Asthma Survey. The TAHS is a general population-based longitudinal study from early childhood to middle age. Comprehensively documented data collected within TAHS cohort provide a unique opportunity to investigate the role of occupational exposure using lifetime work history calendar with the outcome of Chronic Obstructive Pulmonary Disease (COPD).

4.1 Study design

TAHS was initiated in 1968 in Tasmania, a smallest isolated island state of the Commonwealth of Australia located in the southern part of the Australian mainland. The TAHS is now regarded as worlds' largest and longest-running cohort study that were exclusively investigating respiratory and allergic outcomes. Methodological details of TAHS cohort has been published over the decades (29, 177, 178).

In 1968, TAHS began with the enrollment of all seven-year-old children (n=8,583) who were attending school in Tasmania. This baseline cohort was known as "probands" in the subsequent follow-up. At the baseline survey, the parents of the probands completed a respiratory health questionnaire for their child, and then the children underwent a clinical examination and pre-bronchodilator lung function measurements. Subsequent follow-up surveys were completed in 1974, 1979, 1991, 2002 and 2010 at the ages of 12, 18, 30, 45 and 50 years. In 2002 and 2005, when the probands were in their fifth decade of life, 7,562 (88.1%) of the original 1968 probands were retraced to a residential address and achieved a response of 5,729 (78.4%) to a postal survey. A subgroup of these respondents, selected from their participation in previous follow-ups, was invited to participate in a more detailed laboratory study and information was collected using questionnaire, pre, and post-bronchodilator lung function test, skin prick testing, lung volumes, diffusing capacity and lifetime work history calendar. Of 2,387 probands invited (at age 45 years), 1,599 completed work history calendar during laboratory visit or through telephone interview, 1,397 (58.6%)

took part in a full laboratory study, 354 (14.8%) completed the laboratory questionnaire over the phone, and 636 (26.7%) declined to participate. In the 2010 to 2012 period, when the probands were at 50 years of age, participants of 2002 clinical study were re-invited to participate in another laboratory study that includes pre-bronchodilator spirometry and bronchial hyperresponsiveness (BHR) testing. Of the 1,375 eligible participants from the 2002 clinical study, 840 (61.1%) took part in a full laboratory visit, 286 (20.8%) declined to participate, and 249 (18.1%) were not traced. Figure 4.1 describes major follow-ups and laboratory studies within the TAHS cohort. In the following section, I will explain detail methods of TAHS follow-ups that used in my PhD thesis.

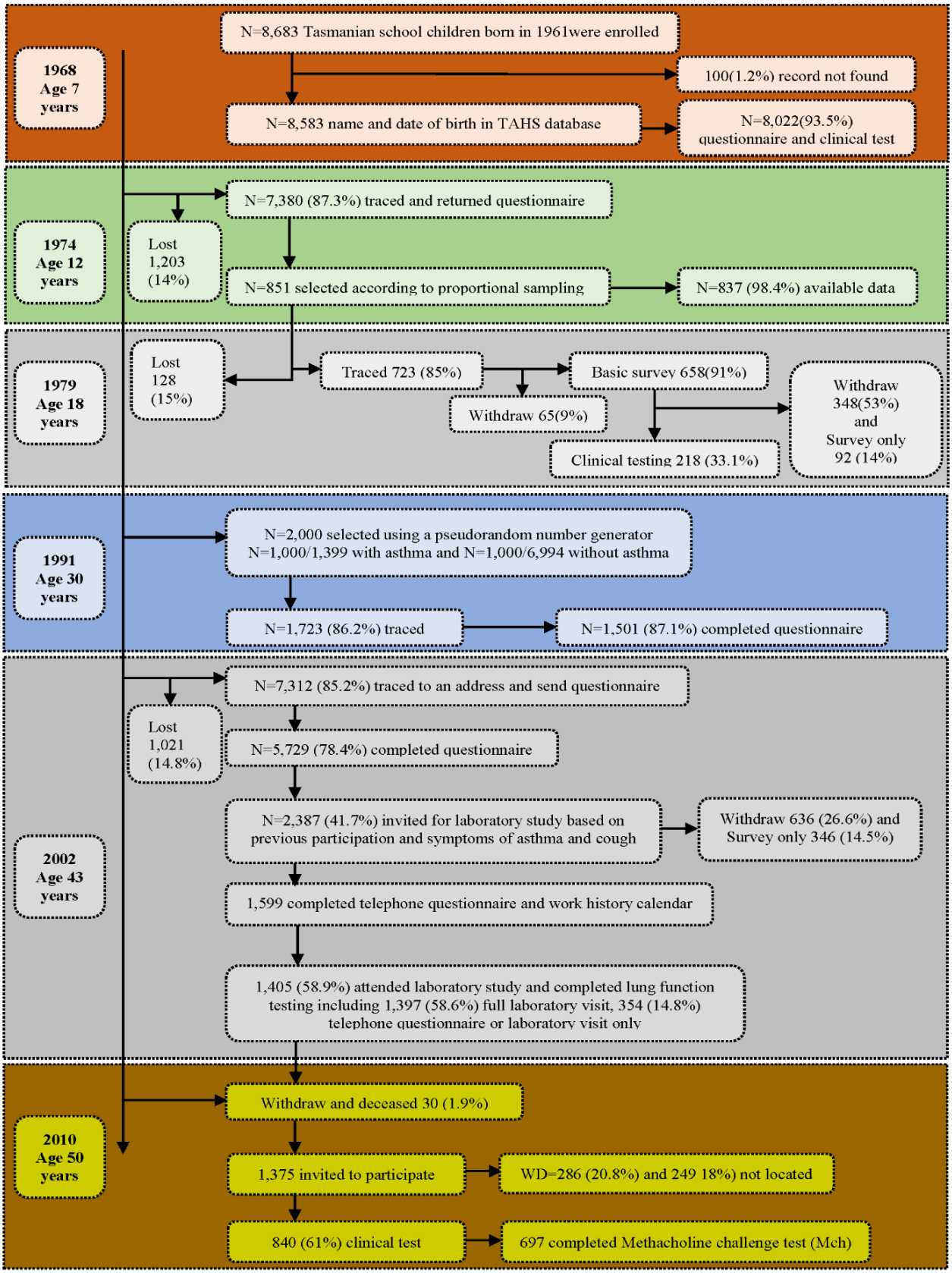


Figure 4.1 The TAHS flow diagram and follow-ups

4.2 Study sample and data collection

4.2.1 The TAHS baseline study in 1968

4.2.1.1 Study sample

As mentioned above, all school children born in 1961 in Tasmania (seven-year-old at the time of survey) were enrolled in TAHS cohort, termed as probands. The names of the children were obtained from the School Health Service Record. All public and private schools in Tasmania agreed to participate and provided the names of all children born in 1961. Seven-year-old school children were chosen to ensure that the child could perform spirometry adequately and to prevent attrition of cohort for several years through the school enrollment system.

4.2.1.2 Data collection

At the beginning of 1968, a set of a questionnaire including a cover letter explaining the aim of the study and consent form were provided to the parents of the probands through the school nurse (Appendix 1). Of the total 8,683 parents of eligible probands to participate in the survey, 8,583 (98.8%) returned a completed questionnaire. Initially, total 273 parents of eligible probands refused to take part in the survey were subsequently re-approached in the same year by the original investigators to reconsider. Children who entered Tasmania after June 1968 were not included in this study.

After the completed questionnaire had been returned, the probands were invited to participate in a detailed laboratory testing that includes complete medical examination and clinical lung function testing. The school medical officer was trained in epidemiological principles, interview technique, and method of objective assessment and also instructed on how to use Vitalograph spirometer. School nurses in Tasmania were also involved in this process under the supervision of the school medical officer.

Each barefooted probands height was measured using a set square and steel measure attached to a wall. The weight of the probands was measured using a reliable set of bathroom scales that calibrated three times daily. Both height and weight were cross-checked by a

second observer to ensure accuracy and validity of the measurements. Total seven Vitalograph spirometers were used to measure lung function, without the inhalation of bronchodilator. The Vitalograph spirometers were regularly calibrated by having an expert normal subject record his/her own ventilatory capacity at regular intervals (178). Two independent observers read the resulted spirograms. The school medical officers also conducted a routine medical examination of the children with particular emphasis on clinical findings in upper airways, chest, and lungs and on evidence of eczema in the flexures of the elbows, wrists, and knees. Of the 8,583 probands who returned completed questionnaires 331 (3.8%) did not attend the laboratory study and 8,022 (93.5%) had complete lung function tests (29).

4.2.2 The TAHS 1974 follow-up study

4.2.2.1 Study sample

The members of 1968 baseline cohort who are still attending school in Tasmania were included in another follow-up study in 1974 at the age of 12 years.

4.2.2.2 Data collection

Total 7,380 (87.2%) participants were retraced and responded to a postal survey questionnaire (Appendix 2). Of these 7,380, a stratified random sample of 851 was selected according to the presence of symptoms of cough only, wheeze only, both cough and wheeze, and neither symptoms in 1968 and 1974 for a clinical follow-up including spirometry. Of these selected 851, almost 98% (837) were attended to a laboratory study to complete spirometry (29).

4.2.3 Proband 2002 to 2008 follow-up study

4.2.3.1 Study sample

This follow-up was conducted between the 2002 to 2008 period when the participants were in their fifth decade of life (Figure 4.1). This follow-up was initially aimed to re-trace the residential addresses of the baseline 1968 cohort and to conduct a postal survey. As the current addresses were last recorded during 1968 baseline survey and the entire cohort had not been followed up since 1968, re-tracing of the original participants in 2002 were

conducted using computerized record linkage. Name, sex and date of birth of the participants were used to identify current address via National Death Index (NDI); the Commonwealth Electoral Roll; the Medicare database; the Tasmanian marriage records; and Twin Research Australia (TRA) (177). In brief, Australian Institute of Health and Welfare (AIHW) assisted TAHS probands data linkage with NDI. Three rounds of data matching were performed using the Commonwealth Electoral Roll database for the probands. TAHS female participants not traced in the previous round of electoral roll was linked to the Tasmanian marriage records to identify a change in surname. Then female participants with the new surname again linked to the electoral roll. A linkage of TAHS probands was conducted using the Health Insurance Commission (HIC), who contacted and agreed to send out mails on behalf of TAHS to identified addresses of the probands. ATR that stores data on 30,000 twin pairs was contacted to identify twins of TAHS cohort using the name and date of birth collected at 1968 baseline survey. Finally, those participants were not found using the above methods; the addresses collected during 1991-93 follow-up survey were checked against the National Electronic White Pages to determine if they were current address.

This follow-up study includes a postal survey of all traced participants from 1968 cohort (mean age 42.8 years) and a laboratory study from a selected subsample of participants (mean age 45 years). From the original 1968 cohort, 7,562 (88.1%) were traced to an address and 5,729 (78.4%) responded (67% from the original 1968 cohort) to a detailed respiratory postal survey questionnaire (Appendix 2). A subgroup of these probands (n=2,387) was selected based on their participation in previous follow-ups and enriched for asthma and cough reported at 1968 or in 2004 postal survey were invited to participate in a more detailed laboratory study conducted between October 2006 to September 2008. Of the 2,387 invited, 1,599 completed work history calendar during laboratory visit or through telephone interview, 1,405 (58.9%) took part in a full laboratory visit (Appendix 3), 346 (14.5%) completed a telephone-administered questionnaire, and 636 (26.6%) withdrew from the study. The mean age of the participants during the laboratory visit was 45 years, and the follow-up was defined as 45-year follow-up study.

4.2.3.2 Data collection-clinical study

Skin prick testing (SPTs) were completed for 1,396 (97.5%) for eight aeroallergens. A wheal size of ≥3mm to a specific allergen more than the negative control was regarded as an indication of sensitization. Blood samples were also drawn for genetic testing. Details of SPT and genetic analysis have been published elsewhere (179).

Of the 1,405 (58.9%) participants attended the laboratory visit, 1,397 (97.7%) had lung function testing. Lung function tests were conducted between 2006 to 2008 under the guidance of A/Prof David Johns, and same protocols (same as 1968 baseline survey) were used across the Australian testing states of Tasmania (81%), Victoria, New South Wales and Queensland. These lung function tests include pre- bronchodilator and post-bronchodilator spirometry, measurement of single breath $D_L$co, and static lung volume measurements, and were conducted according to the joint American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines (40, 180, 181). Details of lung function testing have been described in section 4.4.

4.2.4 Proband 2010 to 2012 follow-up study

4.2.4.1 Study sample

This follow-up was conducted between the 2010 to 2012 by re-inviting the participants from the laboratory study of 45-year follow-up to take part another clinical study that included positive bronchial challenge test. Of the 1,397 eligible participants from the previous follow-up, 840 (61.1%) participated in a laboratory study, 286 (18.1%) declined to participate, and 249 (18.1%) were not located. A small number of participants had died (n=12, 0.9%) or withdrawn (n=18, 1.3%) from the TAHS cohort before the study commenced. The mean age of the participants during the laboratory visit was 49.6 years, and the follow-up was defined as BHR follow-up study.

4.2.4.2 Data collection

The probands who participated in the laboratory study completed a detailed respiratory questionnaire (Appendix 4) and lung function testing including Methacholine

challenge test. Methacholine challenge test was completed by 697 participants. Detailed of lung function testing was described in section 4.3.

4.3 Lung function measurements

4.3.1 Lung function in proband 2002 to 2008 clinical study

Pre and post-bronchodilator spirometry was measured with the EasyOne ultrasonic spirometer (ndd, Medizintechnik, AG, Switzerland). Each of the probands was required to perform at least three pre- and post-bronchodilator spirometry measurements according to the joint ATS and ERS acceptability and repeatability criteria (40, 181). Probands were asked not to smoke for 4-6 hours before testing. Spirometry was repeated 10-15 minutes after short-acting bronchodilator (200μg salbutamol) administration via a spacer. The highest readings for forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were obtained from three acceptable and repeatable tests (40). Each barefooted probands height was recorded to the 0.1 millimeters accuracy at the testing.

Single breath diffusion capacity of the lung for carbon monoxide (D_LCO) was measured post-bronchodilator according to international guidelines and adjusted to a standard hemoglobin concentration and corrected for the presence of carboxyhemoglobin (180). The average of two acceptable tests that agreed to within 10% was recorded. Predicted values of D_LCO for 1,200 subjects were calculated using the prediction equations of Roca and colleagues (182) for age, sex, height and weight covariates for women and by the equations of Thompson and colleagues (183) for an additional former smoker covariates for men.

Z-score values for FEV_1, FVC, and FEV_1/FVC ratio were calculated from the Global Lung Function Initiative (GLI-2012) regression equations (48). A z-score is the deviation from the mean predicted value, where 95% of normally distributed population mean lies between –1.96 standard deviation (SD) to +1.96 SD. In other words, a positive z-score indicates the data point is above the population mean whereas a negative z-score indicates the data point is below the population mean. For example, if the z-score of the FEV_1 = -1.0, that signifies that the FEV_1 is less than the mean of the reference population (184).

4.3.2 Lung function and methacholine challenge test in proband 2010 to 2012 clinical study

Methacholine challenge test was completed by 697 participants in this follow-up. For the methacholine challenge test (Mch), methacholine chloride (Provocholine®, USP Methapharm Inc, Brantford, Ontario, Canada) was administered via a Mefar MB3 inhalation dosimeter (Mefar SRL, Bovezzi, Italy) until FEV_1 fell to less than 80% of the baseline FEV_1 or the maximum cumulative dose of 2mg inhaled. Spirometry in both follow-ups and methacholine challenge test were completed by 797 and 697 subjects, respectively. Log Dose-Response Slope (Log DRSlope) was calculated by log transformation of dose response slope calculated as fall of FEV_1 from baseline of ≥20% divided by maximum dose of methacholine administered (μmol). Due to the Methacholine challenge test only pre-bronchodilator spirometry was performed at the proband 2010 follow-up study. Lung function measurement was performed using the same methods described in section 4.3.

4.4 TAHS Lifetime Work History Calendars data and occupational exposure

4.4.1 Lifetime Work History Calendars

Probands who attended in the laboratory visit of 2002 to 2008 follow-up study also completed a lifetime work history calendar (WHC) (Appendix 5). A total of 1,599 probands provided complete work histories either during laboratory visit or through telephone questionnaire (Figure 4.2). In the WHC, participants were asked to list all the jobs they had held in their lifetime including job held for at least one month from the beginning of the working life up to the date of interview. All different activities held during professional life were also listed, such as unpaid jobs, unemployed, pensioner, homemaker, student, and volunteer work. For each of the job episodes the WHC collected information about (I) job title (e.g., teacher, nurse, manager, student, accountant, chef, engineer, etc.), (II) industry description (e.g., education, retail, mining, health, food, public service, banking, etc.), (III) name of employer, (IV) number of days worked per week, (V) number of hours worked per day, (VI) year work started, and (VII) year work ended. Any changes during working life including any inactivity period were also listed. Around 8,500 jobs from the probands dataset were coded.

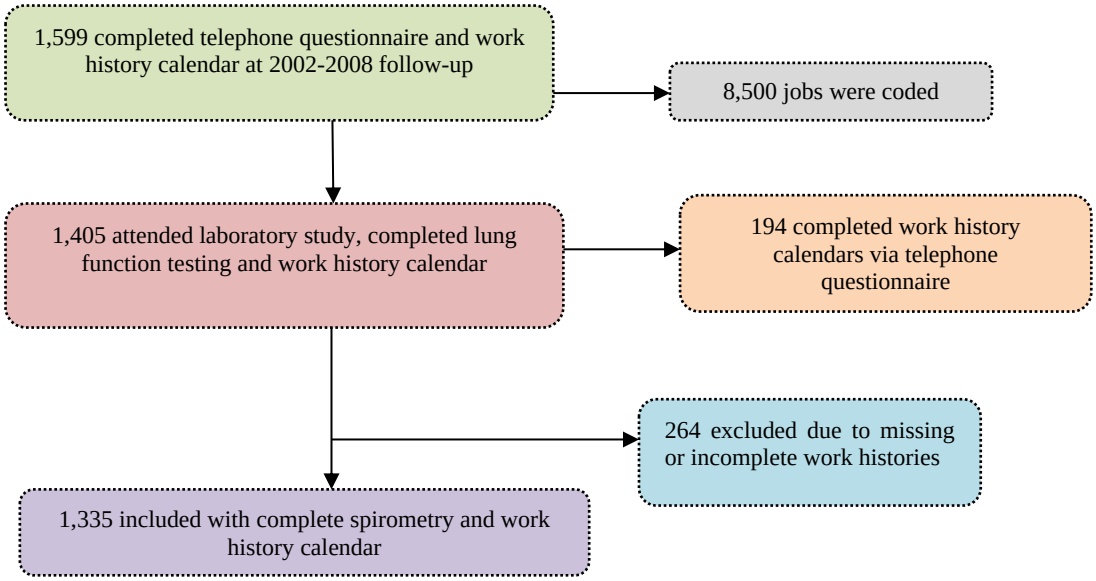


Figure 4.2 Work History Calendar in TAHS proband in 2002 to 2008 follow-up study

4.4.2 Job coding

For each participant, all jobs held during the entire working life were coded according to the International Standard Classification of Occupations (ISCO-88) four-digit classification (30). I performed job coding of the proband dataset under the supervision of Dr Geza Benke. Before starting the job coding, I received special training from Dr Geza Benke and Associate Professor Melanie C Matheson to ensure standardized occupational coding, and I was blind to case status of TAHS dataset before and at the time of coding.

International Standard Classification of Occupations (ISCO-88) of International Labour Organization (ILO) provides a systematic classification and aggregation of occupational information covering the entire working population. ISCO-88 is a revision of ISCO-68 version, which it supersedes and it is one of the standard skill based occupational models of ILO. The design of ISCO-88 was based on two major components; (I) Job- defined as a set of task or duties executed or meant to be executed by a person, and (II) skill- defined

as the ability to carry out the tasks and duties of a given job. On the basis of skill and educational categories from the International Standard Classification of Education (ISCED), four subjective skill levels (first ISCO skill level, second ISCO skill level, third ISCO skill level and fourth ISCO skill level) were defined. Based on the skill levels of technical criterion, codes were established that allows a hierarchical occupational classification that consists of ten major groups that further subdivided into 28 sub-major groups, 116 minor groups, and 390-unit groups. The first one-digit code represents the major group that includes all possible occupations from the general population (Table 4.1). Sub-major groups are two-digit codes, where first digit represents the major group where the 28 sub-major group falls. Minor groups are identified by three-digit codes, where the first two digits indicate the major group where the minor group falls. These minor groups take into account workers tasks, kinds of goods and service produced and differ according to the technical level required. The 390-unit groups represent more detailed groups of occupations that are similar to the job characteristics. They are identified by code numbers of four-digits, where the first two represent the minor group to which the unit group belongs.

Table 4.1 ISCO-88 occupational classifications

Major groups	**Summary of major groups**	**Sub-major groups**	**Minor groups**	**Unit groups**
1. Legislators, senior officials, and managers	Determining and formulating government policies, laws, and public regulations	3	8	33
2. Professionals	High level of professional knowledge and experience in life sciences, social sciences, and humanities	4	18	55
3. Technicians and associate professionals	Technical knowledge and experience in life sciences, social sciences and humanities	4	21	73
4. Clerks	To organize, store, compute and retrieve information for secretarial duties, word processing, office machines or computing numerical data	2	7	23
5. Service workers and shop and market sales workers	To provide personal protective services, and to sell goods to shops, markets, travel agencies, housekeeping, catering and personal care	2	9	23
6. Skilled agricultural and fishery workers	To produce farm, forestry and fishery products including growing crops, breeding or hunting animals, catching or cultivating fish, conserving, exploiting forests, selling agriculture or fishery products	2	6	17
7. Craft and related trade workers	Extracting raw materials, constructing buildings and making various handicraft goods	4	16	70
8. Plant and machine operators and assemblers	To operate and monitor large scale, highly automated, industrial machinery and equipment	3	20	70
9. Elementary occupations	To use hand-held tools, selling goods in streets, doorkeeping, cleaning, washing, pressing, laborers in mining, agriculture, fishery, construction, and manufacturing	3	10	25
0. Armed forces	A person currently servicing armed forces, including auxiliary services, voluntary or compulsory basis and not free to accept civilian employment. Included regular members of army, navy, air forces and other military services	1	1	1
Totals		28	116	390

4.4.3 Occupational exposure assessment

Each of the ISCO-88 coded jobs was linked to general population-based Job Exposure Matrix (JEM) to assess occupational exposure (65). These codes were then used to establish occupational exposures to biological dust, mineral dust, gases/fumes, VGDF (vapors, gases, dusts, or fumes), all pesticides, herbicides, insecticides, aromatic solvents, chlorinated solvents, other solvents and metals using a modified version of the ALOHA JEM for COPD called the ALOHA plus JEM (Table 4.2) (85). The ALOHA plus JEM assigned exposure based on four-digit unit groups of ISCO-88. Each of the coded jobs were classified into no (0), low (1), or high (2) exposure categories based on ALOHA plus JEM (19). In this thesis, a subject was considered occupationally exposed to a substance if at least one of his/her jobs was defined as either low (1) or high (2) exposure by the JEM, by combining low and high exposure categories. Similarly, a subject was defined as non-exposed if none of his/her jobs was ever exposed to any of the occupational agents. Any lifetime exposure was calculated by summing exposures over all job for each participant.

Table 4.2 An example of ALOHA plus JEM based occupational classification

4-digit unit codes of ISCO-88	Job descriptions	ALOHA plus JEM occupational exposures					
		Biological dust	**Mineral dust**	**Gases/ fumes**	**VGDF**	**Pesticides**	**Solvents**
2222	*Dentist*	1	0	0	1	0	0
2422	*Judge*	0	0	0	0	0	0
6111	*Field crop and vegetable growers*	1	2	1	2	2	1
6112	*Tree and shrub crop growers*	1	2	1	2	2	0
7121	*Builders*	2	0	0	2	0	0
7136	*Plumbers and pipe fitters*	0	1	2	2	0	1
7212	*Welders and flame cutters*	0	2	2	2	0	0
8324	*Heavy truck and lorry drivers*	0	1	2	2	0	0

*0=no exposure, 1=low exposure and 2=high exposure

4.4.3.1 Missing job histories

If the participants did not complete the work history calendar, this was counted as missing job history during the preparation of the dataset. This missing information includes missing job title, industry description or name of the company, year work started or ended. These missing job histories were analyzed in different ways during data analysis. If participants job title or industry description was missing, this was initially marked as “no exposure” to any of the occupational agents. Later, a sensitivity analysis was conducted by including these missing job title. In the case of participants having missing information in year work started or ended, this was excluded from the cumulative exposure analysis. This was necessary because cumulative exposure was calculated using year work ended and

started and if any of this information is missing, it was not possible to calculate year of exposure from a particular job. Overall, 120 participants with 314 jobs were found with missing job histories out of a total 1,599 participants over 8,000 jobs.

4.4.3.2 Overlapping jobs

In the case of participants that had two different jobs exist in the same time frame, for example if "job A" was started in 2002 and finished in 2004 and "job B" was started in 2004 and finished in 2006, then the exposures from both job A and job B were averaged and allocated half of the exposure (for low exposure, it was 0.5=1, and for high exposure, it was 1.5=2). However, checks were done to ensure that the hours and days per week for that particular year, between all the jobs, did not exceed the maximum cut-off which was 12 hours per day, 84 hours per week.

4.4.3.3 Years worked in a job

The years worked by the participants in a particular job was calculated by using the year started and year ended provided in the work history calendar. The year started was deducted from the year ended and then "1" was added with that results to calculate years worked in a particular job. For example, if a participant has a job which started in 1980 and then ended in the same year (1980) then the years worked in that job would be 1. Similarly, if a participant was involved in a job from 1980 to 1983, this was counted as four years. This is because it is unknown when a job starts and another one ends in a particular year. The following formula was used to calculate years worked:

$$\text{Years worked} = (\text{year ended} - \text{year started}) + 1$$

4.4.3.4 Cumulative exposure-unit years calculation

The ALOHA plus JEM was also used to calculate cumulative exposures in years by multiplying the number of years worked (y) multiplied by the exposure intensity (i) (i.e. low or high exposure) for each job period (i) and then summed for each participant over the entire job history. To allow for the combination of low and high exposure groups, years of exposure were weighted by 4 (exposure intensity) for high exposure and 1 for low exposure (19, 103). Cumulative exposure-unit years was calculated by using following formula:

$$\text{Cumulative exposure} - \text{unit years for } \textbf{high biological dust exposure} = \sum_i y \times 4$$

$$\text{Cumulative exposure} - \text{unit years for } \textbf{low biological dust exposure} = \sum_i y \times 1$$

4.5 Definitions of the main outcomes

4.5.1 Categorical lung function and respiratory symptoms

Fixed airflow obstruction (AO) was defined according to (1) the Global Initiative for Chronic Obstructive Lung Disease (GOLD) fixed cut-off criterion (post-bronchodilator forced expiratory volume in 1 s over forced vital capacity [FEV_1/FVC] < 0.70) (55) and (2) according to the fifth percentile of the FEV_1/FVC (FEV_1/FVC<lower limit of normal [LLN]) on the basis of prediction equation by Quanjer and colleagues (z-score<-1.64) (48).

Fixed AO plus low D_Lco was defined as post-BD FEV_1/FVC<0.7 and D_Lco <80% of predicted value (19).

Chronic cough was defined by an affirmative response to the question "Do you have cough without a cold on most days for at least three months for at least two years"?

Chronic phlegm was defined by an affirmative response to the question "Do you have phlegm without a cold on most days for at least three months for at least two years"?

Chronic bronchitis was defined by an affirmative response to the question "Do you have cough with phlegm on most days for at least three months of each year for two successive years (55)"?

Dyspnea was defined by an affirmative response to the question "Do you feel shortness of breath when hurrying on level ground or walking up a slight hill"?

4.5.2 Continuous lung function

The rate of pre-BD lung function decline was calculated as FEV_1 (ΔFEV_1), FVC (ΔFVC) and FEV_1/FVC ($\Delta FEV_1/FVC$) divided by the time interval (age in years) between follow-ups in 767 participants who completed lung function measurements in both the 2002 to 2008 and 2010 to 2012 follow-up surveys and who completed a WHC in 2002 to 2008 follow-up survey (Additional details in Chapter 7).

Decline in FEV_1 (ΔFEV_1) was defined as a decrease in the pre-BD FEV_1 (mL/year), compared with the reference group.

Decline in FVC (ΔFVC) was defined as a decrease in the pre-BD FVC (mL/year), compared with the reference group.

Decline in FEV_1/FVC (ΔFEV_1/FVC) was defined as a decrease in the pre-BD **FEV_1/FVC** (%/year), compared with the reference group.

4.5.3 Confounders

4.5.3.1 Directed Acyclic Graph (DAG)

Confounders for the association between occupational exposure and outcomes were selected based on Directed Acyclic Graph (DAG) (Figure 4.3) using DAGitty software (185). DAG provides a graphical and mathematical method to select potential confounders to minimize bias in study design and analysis of epidemiological studies. Potential confounding variables and effect modifiers were selected, either from current literature or from the DAG model below.

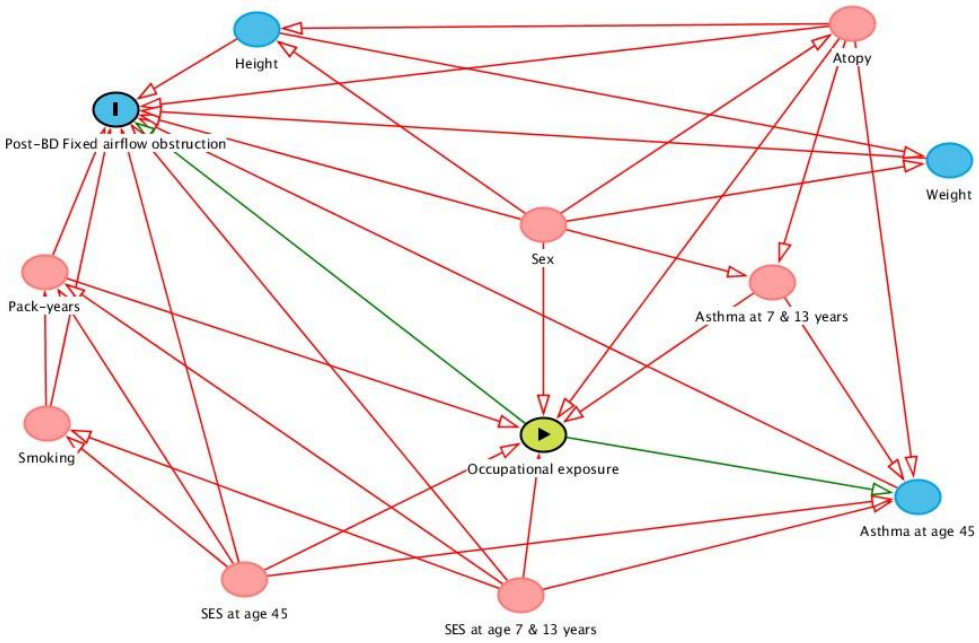


Figure 4.3 DAG for the association between occupational exposure and fixed airflow obstruction (Chapter 5) and (Chapter 6)

4.5.3.2 Definitions of confounders

Asthma was defined by an affirmative response to the question "Have you ever had asthma?"

Current asthma at age 45 years was based on self-reported symptoms in the morning, daytime and nighttime or flare-ups in the last 12 months.

Childhood asthma was defined as asthma reported at age 7 and 12 by an affirmative response by the parents to the question "Has he/she at any time of his/her life suffered from attacks of asthma or wheezy breathing?"

Smoking status of the participants at age 45 and 50 years were categorized as current, past and never-smokers. A current smoker was defined as having smoked in the last four weeks.

Pack-years at age 45 and 50 years were calculated as the number of cigarettes smoked per day divided by 20 multiplied by the number of years of smoking (19).

Socioeconomic status Childhood and adulthood socioeconomic status were defined using Australian census data of Socio-Economic Indexes for Areas (SEIFA indexes) (186). Index of Education and Occupation (IEO) variables that focused on the skills of the people required in different occupations were used to define socioeconomic status at age 7, 12 and 45 years. A high IEO score indicated that people who lived in that area had high qualifications and highly skilled jobs.

Sampling weight The sampling weight variable was derived from the unweighted prevalence of asthma and chronic bronchitis from the 1968 baseline and proband 2002 to 2008 follow-up survey. This variable was used to calculate prevalence and adjusted for the enriched sample of the laboratory study for the regression analysis.

4.6 Statistical analyses

All the statistical analyses were performed using Stata 13.1 (Stata Corporation, College Station, Texas, USA) statistical software. The population prevalences of categorical outcomes and exposures were estimated as observed proportions with 95% confidence intervals (CI) based on the binomial distribution. The associations between categorical outcomes and occupational exposure variables were estimated using multinomial logistic regression models. Occupational exposures and its association with continuous lung function

were analyzed using multivariable linear regression models. For multinomial logistic regression models, sex, smoking, pack-years, asthma in childhood and adulthood, and socioeconomic status in childhood and adulthood were included as a priori confounders. For longitudinal analysis using multivariable linear regression models as reported in Chapter 7, height was considered as an additional confounder. Models that included VGDF, gases/fumes, mineral dust and biological dust as exposure variables were also adjusted for all pesticides as an additional exposure variable. Similarly, models that included all pesticides, herbicides, and insecticides were also adjusted for VGDF exposure due to the presence of co-exposure effect between specific group of exposures. Both the estimated prevalences and the effect estimates from the linear (co-efficient) and logistic regression (relative risk) models were calculated using inverse-probability-of-inclusion weights to adjust for the stratified sampling of the 2002 to 2008 follow-up.

Potential effect measure modification were also investigated based on the biological plausibility of the associations and results were stratified if the effect modification was present. The effect modification was assessed with sex, smoking, and current asthma status by including interaction terms (occupational exposure×sex, occupational exposure×smoking, occupational exposure×current asthma) in the models. A test of effect modification further requires comparing two models, the first (Model 1) with variables A and B entered as main effects but no effect modification, and the second (Model 2) first with variables A and B entered as main effects with the A×B effect modification. Both models were also compared using likelihood ratio test and bayesian information criterion. Some of the analysis were stratified by sex, because of sex-related differences between occupational exposures and lung function. A p-value$\leq$0.05 was considered statistically significant. Specific details of individual analyses have been described in the separate result chapters.

4.7 Ethics

The 2002 to 2008 and 2010 to 2012 follow-ups was approved by the human ethics review committees at the University of Melbourne (approval number 040375), Tasmania (040375.1) and New South Wales (08094), the Alfred Hospital (1118/04), and Royal Brisbane and

Women's Hospital health service district (2006/037) and conducted in accordance with the amended Declaration of Helsinki. Written informed consent was provided for all participants.

Chapter 5 Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age

5.1 Chapter introduction

This publication with additional data supplement investigated the association between occupational exposure assessed by the ALOHA plus JEM and COPD as defined by fixed AO in the middle-aged adult (187). This paper provides evidence that both ever and cumulative exposure to pesticides and herbicides were significantly associated with fixed AO, chronic bronchitis, and respiratory symptoms. In addition, I also found a significant association between ever exposure to mineral dust, gases/fumes and VGDF and fixed AO but only in non-asthmatics but not in asthmatics.

I was the first author for this manuscript. The abstract of this paper has been presented at the American Thoracic Society (ATS) 2016 International conference at San Francisco, United States (188). This paper was also selected as a highlight in the "health article" section of the "Reuters Health" online media (189).

5.2 Research questions and aims

5.2.1 Research questions

1. What is the association between occupational exposure and COPD as defined by post-BD spirometry, chronic bronchitis and respiratory symptoms?
2. Is the effect of occupational exposure and COPD have been modified by sex, smoking, and asthma?

5.2.2 Aims

1. To investigate the relationship between occupational exposure and fixed AO.
2. To study the relationship between occupational exposure and chronic bronchitis, and respiratory symptoms.
3. To examine the potential effect modification by sex, smoking, and asthma on these associations.

5.3 Publication

5.3.1 Main document and online data supplement

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret J, Lodge C, Morrison S, Johns D, Giles G, Gurrin L, Thomas P, Hopper J, Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Walters H, Abramson M, Matheson M. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle age. *Thorax* 2017 doi: 10.1136/thoraxjnl-2016-209665 (In press)

ORIGINAL ARTICLE

Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age

Sheikh M Alif,[1] Shyamali C Dharmage,[1,2] Geza Benke,[3] Martine Dennekamp,[3,4] John A Burgess,[1] Jennifer L Perret,[1,5] Caroline J Lodge,[1] Stephen Morrison,[6] David Peter Johns,[7] Graham G Giles,[1,2,8] Lyle C Gurrin,[1,2] Paul S Thomas,[9] John Llewelyn Hopper,[1] Richard Wood-Baker,[7] Bruce R Thompson,[10] Iain H Feather,[11,12] Roel Vermeulen,[13] Hans Kromhout,[13] E Haydn Walters,[1,3,7] Michael J Abramson,[3] Melanie Claire Matheson[1,2]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2016-209665)

For numbered affiliations see end of article.

Correspondence to
Professor Shyamali C Dharmage, Head of the Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Level 3, 207 Bouverie St, Carlton 3010; s.dharmage@unimelb.edu.au

Received 2 November 2016
Revised 24 April 2017
Accepted 1 May 2017

ABSTRACT

Rationale Population-based studies have found evidence of a relationship between occupational exposures and Chronic Obstructive Pulmonary Disease (COPD), but these studies are limited by the use of prebronchodilator spirometry. Establishing this link using postbronchodilator is critical, because occupational exposures are a modifiable risk factor for COPD.

Objectives To investigate the associations between occupational exposures and fixed airflow obstruction using postbronchodilator spirometry.

Methods One thousand three hundred and thirty-five participants were included from 2002 to 2008 follow-up of the Tasmanian Longitudinal Health Study (TAHS). Spirometry was performed and lifetime work history calendars were used to collect occupational history. ALOHA plus Job Exposure Matrix was used to assign occupational exposure, and defined as ever exposed and cumulative exposure unit (EU)-years. Fixed airflow obstruction was defined by postbronchodilator FEV_1/FVC <0.7 and the lower limit of normal (LLN). Multinomial logistic regressions were used to investigate potential associations while controlling for possible confounders.

Results Ever exposure to biological dust (relative risk (RR)=1.58, 95% CI 1.01 to 2.48), pesticides (RR=1.74,95% CI 1.00 to 3.07) and herbicides (RR=2.09,95% CI 1.18 to 3.70) were associated with fixed airflow obstruction. Cumulative EU-years to all pesticides (RR=1.11,95% CI 1.00 to 1.25) and herbicides (RR=1.15,95% CI 1.00 to 1.32) were also associated with fixed airflow obstruction. In addition, all pesticides exposure was consistently associated with chronic bronchitis and symptoms that are consistent with airflow obstruction. Ever exposure to mineral dust, gases/fumes and vapours, gases, dust or fumes were only associated with fixed airflow obstruction in non-asthmatics only.

Conclusions Pesticides and herbicides exposures were associated with fixed airflow obstruction and chronic bronchitis. Biological dust exposure was also associated with fixed airflow obstruction in non-asthmatics. Minimising occupational exposure to these agents may help to reduce the burden of COPD.

Key messages

What is the key question?

► What are the associations between occupational exposure and fixed airflow obstruction?

What is the bottom line?

► This study has shown that pesticides and herbicides exposures were associated with fixed airflow obstruction, chronic bronchitis and respiratory symptoms.

Why read on?

► This study is the first to describe an association between all pesticides exposure and fixed airflow obstruction, and certain exposures were only associated with fixed airflow obstruction in non-asthmatics but not in asthmatics.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) characterised by postbronchodilator (BD) fixed airflow obstruction (AO) is a chronic debilitating respiratory condition and a growing cause of mortality and morbidity worldwide.[1] Tobacco smoking remains the predominant risk factor for COPD.[2] However, it is now well established that non-smokers also develop COPD and the interest in non-smoking-related risk factors for COPD have exponentially increased in the recent past.[3] Occupational exposures are an important potentially modifiable risk factor for COPD, and while the population-based studies conducted to date have provided valuable information about the importance of these exposures in COPD they have had some important limitations.

We recently performed a systematic review assessing the association between occupational exposure to dusts, gases and fumes, and COPD in population-based studies that used job exposure matrices.[4] Our review found an overall association between occupational exposures to mineral dust and gases/fumes and COPD. However, the results varied by definitions of COPD and only one study to date had used post-BD spirometry to define COPD.[5] This is an important limitation in the current literature as the post-BD measurement of AO is the gold standard to define fixed AO,[6] which is the hallmark feature of COPD.[1] The one study that did use post-BD to define AO did not find any

To cite: Alif SM, Dharmage SC, Benke G, *et al*. *Thorax* Published Online First: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2016-209665

association between dust, gases/fumes and fixed AO.[5] However, the age range of this cohort was very broad and more than a quarter of the cohort were younger than 45 years. This highlights a further limitation of the existing studies in this area; they are relatively young cohorts who are not likely to have developed significant fixed AO. Furthermore, only few population-based studies have investigated the effects of lifetime occupational exposures assessed over an individual's complete working life,[5 7 8] which allows for assessment of cumulative exposure.[9] Our systematic review concluded that the combination of young cohorts with pre-BD lung function and the lack of assessment of lifetime occupational exposures highlight the need for further studies in this area addressing these issues.

Another limitation of the existing literature around occupational exposures and COPD is the lack of studies examining pesticide exposures. There is increasing evidence that pesticide exposure is associated with respiratory symptoms and diseases, with the strongest evidence for asthma.[10 11] Recent studies from the Netherlands have found an association between pesticide and COPD,[12] and lung function decline.[13] However, these studies are again limited by the use of pre-BD spirometry, which does not allow for the identification of fixed AO.

Given the limitations in the studies conducted to date, we investigated the association between occupational exposure and COPD using post-BD spirometry in a general population. We explored both ever exposure and cumulative exposure unit (EU)-years of occupational exposure. Some of the results of this study have been previously published in the form of an abstract.[14]

METHODS

Study design and participants

We included participants from the 2002 to 2008 follow-up of the population-based Tasmanian Longitudinal Health Study (TAHS), details of which have been reported elsewhere,[15] and are summarised in figure 1. Briefly, TAHS started in 1968 when all children aged 7 years (n=8583) attending school in Tasmania were enrolled in a study of asthma. Their parents completed a respiratory health questionnaire, and the children underwent a clinical examination and lung function measurements. Follow-up surveys were conducted in 1974, 1979 and 1991 at the ages of 12, 18 and 30 years, respectively. The 2002–2008 follow-up started in 2002 when participants were in their fifth decade of life. We traced 7562 (88.1%) of the original 1968 cohort to a residential address and achieved a response of 5729 (78.4%) to a postal survey. A subgroup of these respondents, selected from their participation in previous follow-ups and enriched for participants with a history of asthma and bronchitis, were invited to participate in a more detailed laboratory study and information was collected using questionnaire, pre-BD and post-BD lung function test, skin prick testing, lung volumes and diffusing capacity. Of 2387 invited, 1397 (58.6%) took part in full laboratory testing, 354 (14.8%) completed a telephone questionnaire only and 636 (26.7%) withdrew from the study. The 2002 to 2008 follow-up was approved by the Human Research Ethics Committee of the University

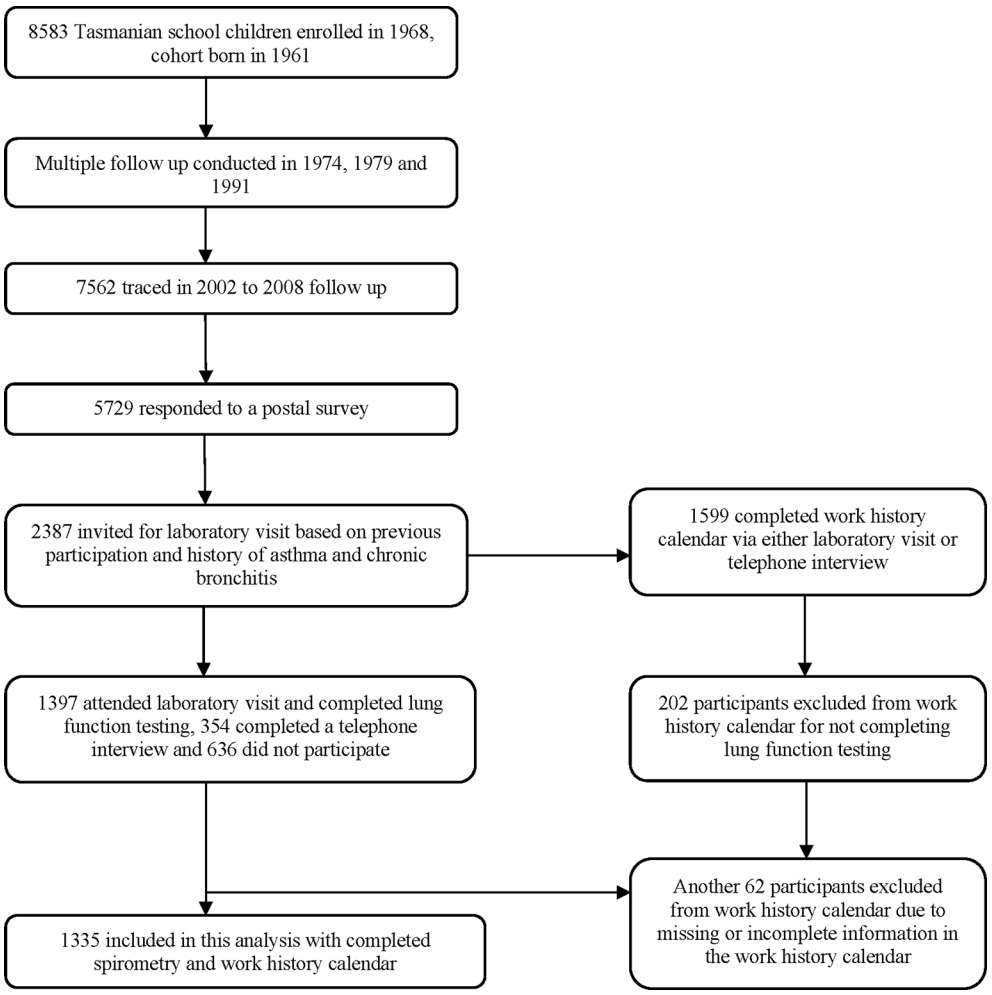


Figure 1 Tasmanian Longitudinal Health Study flow diagram.

of Melbourne (HREC no. 040375). All participants provided written informed consent.

Data collection

Pre-BD and post-BD lung function was measured with the Easyone Ultrasonic spirometer (ndd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4–6 hours before testing. FEV_1 and FVC were measured according to international guidelines and the highest value for FEV_1 and FVC obtained from three acceptable and repeatable tests was recorded.[16] Spirometry was repeated 10–15 min after short-acting bronchodilator (200 μg salbutamol) administration via a spacer.

Outcome definitions

Fixed AO was defined according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: ratio of post-BD FEV_1 and FVC (FEV_1/FVC) <0.70.[17] We also used the lower limit of normal (LLN) to define fixed AO, on the basis of Global Lung Function Initiative 2012 regression equations.[18]

- Chronic bronchitis was defined as a cough with phlegm on most days for at least 3 months of each year for 2 successive years.[17]
- Chronic cough was defined as usually cough without a cold on most days for at least 3 months for at least 2 years.
- Chronic phlegm was defined as usually phlegm without a cold on most days for at least 3 months for at least 2 years.
- Dyspnoea was defined as shortness of breath when hurrying on level ground or walking up a slight hill.

Occupational exposures

Occupational exposures were classified using the lifetime work history calendar that was collected from participants during the laboratory visit or telephone interview. A total of 1599 participants provided complete work histories, but this analysis was restricted to 1335 participants who completed both spirometry testing at the 2002 to 2008 follow-up and the work history calendar. Participants were asked to list all the jobs they had held in their lifetime including job title, industry name, employer name, year work started and ended. The job titles reported by the participants were coded according to the International Standard Classification of Occupations-88 four-digit classification.[19] These codes were then used to establish occupational exposures to biological dust, mineral dust, gases/fumes, vapours, gases, dust or fumes (VGDF), all pesticides, herbicides and insecticides using a modified version of the ALOHA Job Exposure Matrix called the ALOHA plus Job Exposure Matrix.[12] The ALOHA plus Job Exposure Matrix classified participants based on job codes into no, low, or high exposure categories. For this analysis, we combined low and high exposure categories because of a small number of participants in the low exposed group limited the statistical analysis. Ever exposure was calculated by summing exposures over all jobs for each participant. In case of participants having two different jobs at the same time, exposures from both jobs were averaged and rounded up to the nearest integer (0.5=1 and 1.5=2).[12]

The ALOHA plus Job Exposure Matrix was also used to calculate cumulative EU- years by multiplying the number of years worked multiplied by the exposure intensity (ie, low or high exposure) for each job and then summed for each participant over the entire job history. To allow for the combination of low and high exposure groups, years of exposure were weighted by four for high exposure and one for low exposure.[5 7] This cumulative EU-years was calculated for each of the exposure types and scaled continuous variable of cumulative exposure per 10 years. Participants missing any years in the lifetime work history calendar were excluded from the cumulative EU-years analysis and so 1255 participants were included in the unadjusted analysis.

Statistical analysis

All the statistical analyses were conducted using Stata V.13.1 (StataCorp, College Station, Texas, USA). The population prevalence of the outcomes were estimated as observed proportions with 95% CI based on the binomial distribution. The estimate prevalences was calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the 2002 to 2008 follow-up. The associations between outcomes and occupational exposures were estimated using multinomial logistic regression models. We adjusted for sex, smoking, pack-years, asthma in childhood and adulthood, and socioeconomic status in childhood and adulthood. Due to the correlation between any VGDF exposure and all pesticides exposure (see online supplementary table 6) all models that examined biological dust, mineral dust, gases/fumes or VGDF exposures were additionally adjusted for ever exposure to all pesticides. Similarly, models examining all pesticides, herbicides or insecticides exposure were additionally adjusted for VGDF exposure.

Effect modification by sex, smoking and current asthma was assessed by including interaction terms (occupational exposure×sex, occupational exposure×smoking, occupational exposure×current asthma) in the models. We performed a multiple imputation analysis to impute the values of missing confounders and compared this analysis with the complete-case analysis. The results of the imputed analysis did not differ from the complete-case analysis and the results of the imputation analysis are presented in online supplementary tables 3, 4 and 5). A p value ≤0.05 was considered to be statistically significant.

RESULTS

Characteristics of study population

A comparison of responders and non-responders to the laboratory study and postal survey for selected characteristics can be found in the online supplementary table 1. Briefly selected characteristics of the participants those who did and did not attend the laboratory study were similar. Table 1 shows the characteristics of included study participants. The mean age of the participants was 44.8 years (±0.8 SD), over half (51.6%) were men, 87.4% were currently employed and 25.1% were current smokers, with a median smoking history of 21 pack-years (Table 1). There was very little difference in the prevalence of fixed AO when using the GOLD (6%; 95% CI 4.8 to 7.6) or LLN (6%; 95% CI 4.8 to 7.5) criteria. The prevalence of chronic bronchitis was 8.6% (95% CI 7.6 to 9.9) and dyspnoea 12.1% (95% CI 10.4 to 14.1). Over 28% of all participants had ever reported asthma.

Ever exposure

Table 2 shows the association between ever exposure and fixed AO, chronic bronchitis and respiratory symptoms. Ever exposed to biological dust was associated with fixed AO (relative risk (RR)=1.58, 95% CI 1.01 to 2.48), while mineral dust was associated with symptoms. Ever exposed to gases/fumes was not associated with fixed AO or symptoms.

Ever exposure to all pesticides was associated with GOLD-defined fixed AO, chronic bronchitis and also with all respiratory symptoms (table 2). Ever exposed to herbicides was also associated with fixed AO, chronic bronchitis and chronic cough. Ever exposed to insecticides was associated with chronic bronchitis and

Table 1 Characteristic of the population

Study characteristics	n (%)*	95% CI
Age, years (mean, SD) (n=1334)	44.8 (0.8)	44.7 to 44.9
Sex, % (n=1335)		
Men	684 (51.6)	48.5 to 54.9
Women	651 (48.3)	45.0 to 51.5
Smoking history (n=1330)		
Never, n (%)	566 (45.3)	42.1 to 48.6
Past, n (%) Pack-years, median (IQR) (n=1292)	394 (29.6) 7.5 (2–17)	26.7 to 32.6
Current, n (%) Pack-years, median (IQR) (n=1292)	370 (25.1) 21 (10–30)	22.4 to 27.9
Currently employed, n (%) (n=1332)	1136 (87.4)	85.2 to 89.3
Fixed airflow obstruction (AO)		
Fixed AO-GOLD (n=1335)	113 (6.0)	4.8 to 7.6
Stage I: FEV_1/FVC <0.7 and FEV_1 ≥80%	62 (3.7)	2.7 to 5.1
Stage II: FEV_1/FVC <0.7 and FEV_1 <80%	51 (2.3)	1.7 to 3.2
Fixed AO-LLN (n=1335)	112 (6.0)	4.8 to 7.5
Chronic bronchitis (n=1322)	246 (8.7)	7.6 to 9.9
Respiratory symptoms		
Chronic cough (n=1316)	185 (8.8)	7.4 to 10.3
Chronic phlegm (n=1317)	171 (6.8)	5.8 to 8.1
Dyspnoea (n=1334)	227 (12.1)	10.4 to 14.1

*The estimated prevalences were calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the fifth decade follow-up survey.
AO, airflow obstruction; GOLD, Global Obstructive Lung Disease; LLN, lower limit of normal.

chronic cough. Using LLN definition of fixed AO (table 2), we found a significant association between ever exposure to herbicides and fixed AO and a trend of association between all pesticides and insecticides and fixed AO. In general, using both definitions, we found both all pesticides and herbicides were associated with fixed AO.

Cumulative EU-years

For every 10-year increase in cumulative EU-years of exposure to biological dust, there was a 7% increase of chronic cough (RR=1.07, 95%CI 1.00 to 1.15). Cumulative EU-years of exposure to mineral dust and gases and fumes were associated with a 5% increase of dyspnoea (table 3). Cumulative EU-years of exposure to all pesticides was consistently associated with both definitions of fixed AO, chronic bronchitis, chronic cough and chronic phlegm. Cumulative EU-years of exposure to herbicides was associated with fixed AO and chronic bronchitis. Cumulative EU-years of exposure to insecticides was associated with 15% increase of chronic bronchitis (RR=1.15, 95%CI 1.02 to 1.29).

Interactions with sex, smoking and current asthma

We explored the potential interactions between occupational exposures and sex, smoking and current asthma. We did not find any interactions with sex or smoking (data not shown). However, we found significant interactions between ever exposure and current asthma. We found a significant interaction between current asthma and biological dust (interaction p=0.003), mineral dust (interaction p=0.03), gases/fumes (interaction p=0.005) and VGDF (interaction p=0.01) for GOLD-defined fixed AO (table 4). For all of these occupational exposures, there was association with fixed AO in the non-asthmatic group but not in the asthmatic group.

DISCUSSION

This is the first study to examine fixed AO using the gold standard measurement of post-BD spirometry and two measures of occupational exposure, ever exposure and lifetime cumulative EU-years. Using these robust measures, we have demonstrated significant and consistent associations between all pesticides exposure, fixed AO, chronic bronchitis and chronic cough. We are the first to show that ever exposure to pesticides is associated with fixed AO and increasing cumulative EU-years to pesticides are associated with fixed AO.

A number of previous workplace-based studies have reported increased prevalence of respiratory symptoms and reduced lung function among farmers or agriculture workers exposed to pesticides.[20–23] However, there has only been one population-based study published in relation to pesticides exposure and AO. This study examined two Dutch cohorts and found an association between pre-BD AO in people exposed to pesticides in one cohort, and a trend towards an association in the other for moderate/severe AO (defined as pre-BD FEV_1/FVC <70% and FEV_1 <80%).[12] Both cohorts in this study used pre-BD spirometry to define AO, which may have overestimated the prevalence of AO. They also used current or last held job and the results may have been confounded by past exposure. We have demonstrated, in a similarly aged population, an association between ever exposure and cumulative EU-years to all pesticides and fixed AO confirming that minimising exposure to all pesticides may help to reduce the burden of COPD.

We also observed significant association between chronic bronchitis, chronic cough and chronic phlegm with both ever exposure and cumulative EU-years to pesticides. We are first to show cumulative EU-years to pesticides is associated with chronic respiratory symptoms in a population-based study. Recent systematic reviews found chronic bronchitis was associated with pesticides exposure[10 24] and a study of the US farmers found association between exposure to pesticides and chronic bronchitis.[20] Similar to our findings, a study from Latin America also found an association between pesticides exposure and respiratory symptoms.[21] However, all these studies were conducted in specific occupational groups making the results not applicable to the broader general population, unlike the results from our study.

Pesticides can be classified according to their targets into three main areas: insecticides, herbicides and fungicides. Insecticides include organochlorines, organophosphates and carbamates. Herbicides include phenoxy herbicides and fungicides include dithiocarbamates, and all have been used extensively in agriculture to control pests and weeds.[10] Pesticides can enter the body through inhalation into the respiratory tract and absorption through the skin during use for fumigation, preparation and spraying or during manufacture, storage or transport.[10 24] Long-term exposure to organophosphate and carbamate pesticides has been shown to lead to inhibition of acetylcholinesterase synthesis from M2 muscarinic receptors that results in mucus hypersecretion and airway smooth muscle contraction causing breathlessness, cough and wheeze.[10 24] The inactive acetylcholinesterase is also responsible for thickening of alveolar-capillary membrane leading to reduced level of lung function.[25]

The ALOHA plus Job Exposure Matrix assigned exposure to pesticides as ever exposure to all pesticides and then also had subcategories of specific herbicides and insecticides exposures.

Table 2 Association between ever exposure and fixed airflow obstruction, chronic bronchitis and respiratory symptoms

	Fixed AO-GOLD			Fixed AO-LLN			Chronic bronchitis			Chronic cough			Chronic phlegm			Dyspnoea		
Exposures	No 1222	Yes 113	RR (95% CI) *	No 1223	Yes 112	RR (95% CI)	No 1075	Yes 246	RR (95% CI)	No 1131	Yes 185	RR (95% CI)	No 1146	Yes 171	RR (95% CI)	No 1107	Yes 226	RR (95% CI)
Biological dust																		
Not exposed	541	37	Ref.	541	37	Ref.	483	87	Ref.	511	59	Ref.	508	61	Ref.	504	74	Ref.
Exposed	681	76	**1.58 (1.01 to 2.48)**	681	75	**1.56 (1.00 to 2.45)**	592	159	0.99 (0.67 to 1.48)	620	126	1.24 (0.83 to 1.84)	639	109	0.98 (0.66 to 1.46)	603	152	1.32 (0.95 to 1.85)
Mineral dust																		
Not exposed	585	42	Ref.	586	42	Ref.	522	98	Ref.	555	64	Ref.	563	57	Ref.	544	84	Ref.
Exposed	636	71	1.29 (0.81 to 2.04)	637	70	1.29 (0.81 to 2.04)	554	148	1.10 (0.72 to 1.67)	576	121	**1.62 (1.06 to 2.48)**	583	114	**1.51 (1.00 to 2.30)**	563	143	**1.57 (1.10 to 2.23)**
Gases/fumes																		
Not exposed	352	22	Ref.	353	22	Ref.	314	57	Ref.	335	33	Ref.	336	33	Ref.	327	48	Ref.
Exposed	869	91	1.50 (0.88 to 2.54)	870	90	1.47 (0.87 to 2.51)	762	189	0.91 (0.58 to 1.45)	796	152	1.25 (0.80 to 1.98)	810	138	1.20 (0.76 to 1.90)	780	179	1.31 (0.89 to 1.91)
VGDF																		
Not exposed	300	21	Ref.	301	21	Ref.	273	45	Ref.	293	23	Ref.	290	26	Ref.	281	41	Ref.
Exposed	921	92	1.29 (0.73 to 2.17)	922	91	1.25 (0.72 to 2.15)	803	201	0.95 (0.58 to 1.55)	838	162	**1.69 (1.01 to 2.84)**	856	145	1.31 (0.80 to 2.17)	826	186	1.29 (0.86 to 1.93)
All pesticides																		
Not exposed	1024	85	Ref.	1024	85	Ref.	916	183	Ref.	961	134	Ref.	971	124	Ref.	940	169	Ref.
Exposed	198	28	**1.74 (1.00 to 3.07)**	199	27	1.63 (0.91 to 3.07)	160	63	**1.81 (1.12 to 2.93)**	170	51	**1.77 (1.04 to 3.01)**	175	47	**2.06 (1.23 to 3.47)**	167	58	**1.95 (1.23 to 3.09)**
Herbicides																		
Not exposed	1061	87	Ref.	1061	87	Ref.	947	191	Ref.	993	141	Ref.	1002	132	Ref.	966	182	Ref.
Exposed	161	26	**2.09 (1.18 to 3.70)**	162	25	**1.95 (1.08 to 3.49)**	129	55	**1.81 (1.08 to 3.02)**	138	44	**1.79 (1.04 to 3.09)**	144	39	1.62 (0.93 to 2.83)	141	45	1.44 (0.89 to 2.34)
Insecticides																		
Not exposed	1060	91	Ref.	1060	91	Ref.	947	194	Ref.	996	141	Ref.	1002	135	Ref.	970	181	Ref.
Exposed	162	22	1.70 (0.93 to 3.10)	163	21	1.56 (0.84 to 2.90)	129	52	**1.64 (1.00 to 2.72)**	135	44	**1.74 (1.00 to 3.05)**	144	36	1.62 (0.93 to 2.84)	137	46	1.58 (0.97 to 2.57)

The bolded text identifies results reaching statistical significance ($p \leq 0.05$).
*Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma. The analyses with biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure.
AO, airflow obstruction;GOLD, Global Obstructive Lung Disease; LLN, lower limit of normal; RR, relative risk; VGDF, vapour, gases, dust and fumes.

Table 3 Association between cumulative EU-years and fixed airflow obstruction, chronic bronchitis and respiratory symptoms (n=1255)

Cumulative exposures	Fixed AO-GOLD		Fixed AO-LLN		Chronic bronchitis		Chronic cough		Chronic phlegm		Dyspnoea	
	RR (95% CI)*	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Biological dust	1.05 (0.97 to 1.13)	0.22	1.03 (0.96 to 1.12)	0.35	1.06 (0.99 to 1.13)	0.07	**1.07 (1.00 to 1.15)**	**0.05**	1.01 (0.94 to 1.09)	0.68	0.99 (0.92 to 1.06)	0.82
Mineral dust	1.03 (0.97 to 1.10)	0.31	1.03 (0.97 to 1.11)	0.28	1.04 (0.98 to 1.11)	0.12	1.00 (0.93 to 1.07)	0.97	1.03 (0.96 to 1.10)	0.36	**1.05 (1.00 to 1.11)**	**0.05**
Gases/fumes	1.02 (0.96 to 1.09)	0.44	1.02 (0.96 to 1.09)	0.51	1.03 (0.97 to 1.09)	0.36	0.97 (0.91 to 1.04)	0.54	1.03 (0.98 to 1.10)	0.23	**1.05 (1.00 to 1.10)**	**0.05**
VGDF	1.02 (0.97 to 1.08)	0.32	1.03 (0.97 to 1.09)	0.33	**1.05 (1.00 to 1.10)**	**0.05**	1.03 (0.97 to 1.08)	0.24	1.03 (0.98 to 1.08)	0.25	1.02 (0.98 to 1.07)	0.25
All pesticides	**1.12 (1.00 to 1.25)**	**0.05**	**1.13 (1.00 to 1.29)**	**0.05**	**1.16 (1.10 to 1.30)**	**0.01**	**1.12 (1.00 to 1.28)**	**0.05**	**1.13 (1.00 to 1.30)**	**0.05**	0.94 (0.82 to 1.08)	0.40
Herbicides	**1.16 (1.00 to 1.32)**	**0.04**	**1.15 (1.00 to 1.36)**	**0.05**	**1.22 (1.05 to 1.41)**	**0.01**	1.12 (0.97 to 1.30)	0.12	1.10 (0.93 to 1.31)	0.23	0.91 (0.77 to 1.09)	0.33
Insecticides	1.10 (0.98 to 1.24)	0.10	1.10 (0.96 to 1.26)	0.19	**1.15 (1.02 to 1.29)**	**0.02**	1.06 (0.92 to 1.22)	0.38	1.13 (0.99 to 1.30)	0.08	0.94 (0.83 to 1.09)	0.51

The bolded text identifies results reaching statistical significance (p≤0.05).
*Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma. The analyses with biological dust, mineral dust, gases/fumes and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides and insecticides were additionally adjusted for VGDF exposure.
AO, airflow obstruction; EU, exposure unit; GOLD, Global Obstructive Lung Disease; LLN, lower limit of normal; RR, relative risk; VGDF, vapour, gases, dust and fumes.

The associations observed in this study were largely consistent across all three categories, with some not quite reaching statistical significance for some symptoms. The possible explanation for this slight variation across the subcategories of all pesticides exposure is differences in exposures between different occupational groups with some groups, for example, cattle farmers not being exposed to herbicides but to insecticides. Another example of this is forestry workers who formed a large proportion of our exposed workers (23.8%), but who had 'all pesticides exposure' and 'herbicides exposure' but not 'insecticides exposure'. Another explanation is the presence of very strong correlation between these exposures (see online supplementary table 6). In our study, participants with high all pesticides exposures included people who described themselves as farm hands/labourers, forestry workers, gardeners, horticultural/nursery workers, and crop/vegetable growers.

For the other common exposures to biological dust, mineral dust and gases/fumes, we only observed association with fixed AO for those ever exposed to biological dust. This finding is consistent with previous studies that have also found association between biological dust and COPD.[7 19] The finding with biological dust in the present study is also consistent with the meta-analysis conducted by our group, although the effect estimates did not reach statistical significance in our meta-analysis.[4] The reason for this slight variation in the effect estimate may be due to the inclusion of pre-BD in most of the included studies in our meta-analysis. We did not observe any association between mineral dust and gases/fumes exposure and fixed AO, but we did observe associations with respiratory symptoms. Several previous studies also found an association between dust exposure in general and respiratory symptoms.[26 27]

Our study observed a significant interaction between current asthma and four of the occupational exposures for fixed AO. In the non-asthmatics, there was an association between ever exposure to biological dust, mineral dust and gases/fumes and fixed AO, even with a low crude prevalence of 7.12% in non-asthmatics, compared with asthmatics (16.98%). We did not observe the same interaction for cumulative EU-years to these agents. This finding is suggestive of a healthy worker effect, that is, asthmatics who remain in the study are relatively unaffected by these occupational exposures. It also may suggest that asthma alone is a significant risk factor for fixed AO in middle-age and additional occupational exposure does not substantially increase the risk observed at this age. We did explore childhood asthma status, recorded prospectively in this cohort, but we did not find any interaction with occupational exposures and fixed AO. We also did not observe any interaction between current asthma and all pesticides for fixed AO suggesting the ever exposure and cumulative EU-years of all pesticides significantly associated with fixed AO independent of asthma.

Previous studies of occupational exposure and COPD using the ALOHA Job Exposure Matrix have taken asthma into account in their analysis by different methods. They have either excluded asthmatics completely[8 19 28] or performed sensitivity analysis to see if excluding participants with asthma influenced the results.[5 7] Including participants with asthma would inflate the prevalence of fixed AO, especially if pre-BD was used in a relatively young cohort, as was the case for several of these studies,[12 28] leading to spurious results. We included both childhood and adult asthma as a confounder in the statistical analyses and investigated the possible interaction with current asthma. Our study has demonstrated for the first time in a general population that asthma significantly modifies the effect of biological dust, mineral dust and gases, and fumes on fixed AO in middle-age.

Table 4 Association between ever exposure to biological dust, mineral dust, gases/fumes and VGDF stratified by current asthma

	Current asthmatics			Non-asthmatics			
	Fixed AO-GOLD			Fixed AO-GOLD			
Exposures	No % (n/N)	Yes % (n/N)	RR (95% CI)	No % (n/N)	Yes % (n/N)	RR (95% CI)	Interaction p Value*
Biological dust	63% (167/265)	55.6% (25/45)	0.68 (0.35 to 1.34)	53.6% (512/955)	75% (51/68)	**2.80 (1.48 to 5.27)**	**0.003**
Mineral dust	56.% (149/266)	53.3% (24/45)	0.70 (0.35 to 1.38)	50.9% (486/955)	69.1% (47/68)	1.80 (0.98 to 3.32)	**0.03**
Gases/fumes	76.3% (203/266)	71.1% (32/45)	0.61 (0.29 to 1.29)	69.6% (665/955)	86.8% (59/68)	**2.92 (1.27 to 6.67)**	**0.005**
VGDF	79.7% (212/266)	73.3% (33/45)	0.57 (0.26 to 1.22)	74.1% (708/955)	86.8% (59/68)	**2.33 (1.01 to 5.34)**	**0.01**

The bolded text identifies results reaching statistical significance (p≤0.05).
*p≤0.05 for the interaction between exposure and current asthma.
†Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and all pesticides as coexposure.
No interaction was observed with exposure to all pesticides, herbicides and insecticides (results not shown).
AO, airflow obstruction; GOLD, Global Obstructive Lung Disease; RR, relative risk; VGDF, vapour, gases, dust and fumes.

Both GOLD and LLN definitions of fixed AO in our study produced similar effect estimates with most of the exposures except all pesticides exposure, where we found a significant association using GOLD definition, but when we used the LLN definition the association with all pesticides did not quite reach statistical significance. The previous study on occupational exposure and COPD in Switzerland also found similar to our results, although they used pre-BD to define COPD.[19] Post-BD is essential to define fixed AO, but there is still debate over the best cut-off values to define fixed AO.[29] The GOLD definition of fixed ratio (FEV_1/FVC <0.7) has been widely used for clinical application as well as large-scale population-based studies.[30 31] More recently, statistical reference equation-based LLN definition also provide an opportunity to overcome age-related overestimation of the total effect by GOLD.[31] We observed very little variation between the two definitions of fixed AO, with only one person being classified as having fixed AO by the GOLD and not the LLN definition. This person was on the borderline of being categorised as having fixed AO by the LLN definition. Other data from this individual (ie, heavy personal smoking history and occupational history with high likelihood of occupational exposure to herbicides and all pesticides) and the relatively small change in the estimates between the two definitions we would not regard this person as an extreme outlier or having undue influence and so he has not been removed from the analysis.

The availability of post-BD data was a major strength of our study. The availability of work history calendars for the participants' entire working life was also a major strength and enabled the calculation of ever exposure and cumulative EU-years. We have attempted to minimise any bias related to recalling of work exposures by using standardised lifetime work history calendars and then assigning exposure via the use of a Job Exposure Matrix to estimate cumulative EU-years across all jobs. Job Exposure Matrices are affected by non-differential misclassification of exposure, which occurs when there is heterogeneity of exposure in a given job or occupation. However, this generally results in misclassification towards the null, leading to an underestimation of the effect of the exposure on risk of the disease. Multiple comparisons were performed but the associations, particularly with all pesticides and herbicides exposure, were consistent across several outcomes, suggesting genuine associations rather than chance findings. However, our laboratory attendees, enriched for asthma and chronic bronchitis and had similar clinical profiles despite the lung function testing.

In conclusion, our study has shown that both ever and cumulative EU-years to pesticides are associated with fixed AO and respiratory symptoms. We have also shown this effect of pesticides is independent of asthma. For other occupational exposures to VDGF, we found an association with fixed AO only in those without current asthma. However, we did not find any significant association between fixed AO, and chronic bronchitis with exposure to mineral dust, gases/fumes and VGDF. Future population-based studies need to use post-BD to define fixed AO, which allows asthma to be adequately taken into account. Our study has shown even in a middle-aged group of people, a significant proportion of fixed AO is associated with occupational exposures. Our findings highlight the need to reduce workplace exposure to pesticides by improving adherence to use of recommended protective equipment, and workplace monitoring of exposure levels could be implemented. By enhanced monitoring and use of protective equipment, the burden of COPD caused by occupational exposures has the potential to be substantially reduced.

Author affiliations
[1]Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia
[2]Murdoch Childrens Research Institute, Melbourne, Victoria, Australia
[3]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia
[4]Graduate Entry Medical School, University of Limerick, Limerick, Ireland
[5]Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, Victoria, Australia
[6]Department of Medicine, University of Queensland, Brisbane, Queensland, Australia
[7]School of Medicine, University of Tasmania, Hobart, Tasmania, Australia
[8]Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, Victoria, Australia
[9]Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia
[10]Allergy Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, Victoria, Australia
[11]Gold Coast University Hospital, Southport, Queensland, Australia
[12]Bond University, Robina, Queensland, Australia
[13]Environmental Epidemiology Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

Acknowledgements We acknowledge the Tasmanian Longitudinal Health Study (TAHS) participants and previous investigators. We thank Professor Mark Jenkins, PhD, Centre Director, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Victoria, who is a TAHS investigator but not a coauthor of this manuscript, for his assistance with obtaining funds and data collection. Furthermore, we acknowledge all the respiratory scientists who

collected data in the lung function laboratories of Tasmania, Victoria, Queensland, and New South Wales; the research interviewers and data entry operators and the organisational roles of Ms Cathryn Wharton and Dr Desiree Mészáros.

Contributors Study concept and design: SMA, SCD, GB, RV, HK, EHW, MJA, MCM. Acquisition of data: SMA, SCD, JLP, PST, RWB, BRT, IHF, RV, HK, EHW, MJA, MCM. Analysis and interpretation of data: SMA, SCD, GB, MD, LCG, RV, HK, MJA, MCM. Drafting of the manuscript: SMA, SCD, GB, MD, MCM. Critical revision of the manuscript for important intellectual content: All Authors. Statistical analysis: SMA, LCG, MCM. Obtained funding: SCD, GB, DPJ, LCG, PST, JLH, RWB, BRT, IHF, EHW, MJA, MCM. Study supervision: SMA, SCD, GB, MD, MCM. SMA and MCM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding Supported by the National Health and Medical Research Council of Australia; Clifford Craig Medical Research Trust of Tasmania; Victorian, Queensland, and Tasmanian Asthma Foundations; and the Australian Lung Foundation. SCD is supported by the NHMRC.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1 Celli BR, Decramer M, Wedzicha JA, *et al*. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. *Eur Respir J* 2015;45:879–905.
2 Balmes J, Becklake M, Blanc P, *et al*. American Thoracic Society Statement: occupational contribution to the burden of airway disease. *Am J Respir Crit Care Med* 2003;167:787–97.
3 Eisner MD, Anthonisen N, Coultas D, *et al*. An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2010;182:693–718.
4 Alif SM, Dharmage SC, Bowatte G, *et al*. Occupational exposure and risk of chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Expert Rev Respir Med* 2016;10:861–72.
5 Hansell A, Ghosh RE, Poole S, *et al*. Occupational risk factors for chronic respiratory disease in a New Zealand population using lifetime occupational history. *J Occup Environ Med* 2014;56:270–80.
6 Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. *Eur Respir J* 2004;23:497–8.
7 Matheson MC, Benke G, Raven J, *et al*. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax* 2005;60:645–51.
8 Würtz ET, Schlünssen V, Malling TH, *et al*. Occupational chronic obstructive pulmonary disease in a danish Population-Based study. *COPD* 2015;12:435–43.
9 Lilley RC, Cryer PC, Firth HM, *et al*. Ascertainment of occupational histories in the working population: the occupational history calendar approach. *Am J Ind Med* 2011;54:21–31.
10 Mamane A, Baldi I, Tessier JF, *et al*. Occupational exposure to pesticides and respiratory health. *Eur Respir Rev* 2015;24:306–19.
11 Hernández AF, Parrón T, Alarcón R. Pesticides and asthma. *Curr Opin Allergy Clin Immunol* 2011;11:90–6.
12 de Jong K, Boezen HM, Kromhout H, *et al*. Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study. *Occup Environ Med* 2014;71:88–96.
13 de Jong K, Boezen HM, Kromhout H, *et al*. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. *Am J Epidemiol* 2014;179:1323–30.
14 Alif SM, Dharmage SC, Benke G, *et al*. Lifetime Occupational exposure to Vapor, gases/Fumes, dust and risk of COPD at 45 years: the Tasmanian Longitudinal Health Study (TAHS) (abstract). *Am J Resp Crit Care Med* 2016;193:A2989.
15 Matheson MC, Abramson MJ, Allen K, *et al*. TAHS investigator group. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). *Int J Epidemiol* 2017;46:407-408i.
16 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
17 Vestbo J, Hurd SS, Agustí AG, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013;187:347–65.
18 Quanjer PH, Stanojevic S, Cole TJ, *et al*. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012;40:1324–43.
19 Mehta AJ, Miedinger D, Keidel D, *et al*. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary disease in the Swiss Cohort Study on Air Pollution and Lung and Heart Diseases in Adults. *Am J Respir Crit Care Med* 2012;185:1292–300.
20 Hoppin JA, Valcin M, Henneberger PK, *et al*. Pesticide use and chronic bronchitis among farmers in the Agricultural Health Study. *Am J Ind Med* 2007;50:969–79.
21 Fieten KB, Kromhout H, Heederik D, *et al*. Pesticide exposure and respiratory health of indigenous women in Costa Rica. *Am J Epidemiol* 2009;169:1500–6.
22 Faria NM, Facchini LA, Fassa AG, *et al*. Pesticides and respiratory symptoms among farmers. *Rev Saude Publica* 2005;39:973–81.
23 Sham'a FA, Skogstad M, Nijem K, *et al*. Cross-Shift changes in lung function among palestinian farmers during high- and Low-Exposure periods to Pesticides: a longitudinal study. *Arch Environ Occup Health* 2015;70:218–24.
24 Doust E, Ayres JG, Devereux G, *et al*. Is pesticide exposure a cause of obstructive airways disease? *Eur Respir Rev* 2014;23:180–92.
25 Peiris-John RJ, Ruberu DK, Wickremasinghe AR, *et al*. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. *Respir Med* 2005;99:1319–24.
26 Marchetti N, Garshick E, Kinney GL, *et al*. Association between occupational exposure and lung function, respiratory symptoms, and high-resolution computed tomography imaging in COPDGene. *Am J Respir Crit Care Med* 2014;190:756–62.
27 Lam KB, Yin P, Jiang CQ, *et al*. Past dust and GAS/FUME exposure and COPD in Chinese: the Guangzhou Biobank Cohort Study. *Respir Med* 2012;106:1421–8.
28 Sunyer J, Kogevinas M, Kromhout H, *et al*. Pulmonary ventilatory defects and Occupational exposures in a Population-based study in Spain. *Am J Respir Crit Care Med* 1998;157:512–7.
29 Swanney MP, Ruppel G, Enright PL, *et al*. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63:1046–51.
30 Cerveri I, Corsico AG, Accordini S, *et al*. Underestimation of airflow obstruction among young adults using FEV1/FVC <70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. *Thorax* 2008;63:1040–5.
31 Roberts SD, Farber MO, Knox KS, *et al*. FEV1/FVC ratio of 70% misclassifies patients with obstruction at the extremes of age. *Chest* 2006;130:200–6.

SUPPLEMENTARY MATERIAL

Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age

Authors

Sheikh M. Alif [1], Shyamali C. Dharmage [1, 2], Geza Benke [3], Martine Dennekamp [3,4], John A. Burgess [1], Jennifer L. Perret [1, 5], Caroline J. Lodge [1], Stephen Morrison [6],David P. Johns [7], Graham G. Giles [1, 2, 8], Lyle C. Gurrin[1, 2] , Paul S. Thomas [9] , John L. Hopper [1], Richard Wood-Baker [7], Bruce R Thompson [10], Iain H. Feather[11,12], Roel Vermeulen [13], Hans Kromhout [13], E Haydn Walters [1, 3, 7], Michael J. Abramson [3], Melanie C. Matheson [1, 2]

SUPPLEMENTARY METHODS

Definitions of confounders

Having had asthma was defined by an affirmative response to the question "Have you ever had asthma?" Current asthma was based on self-reported symptoms in the morning, day-time and night-time or flare-ups in the last 12 months. Childhood asthma was defined as asthma reported at age 7 and 12 by an affirmative response by the parents to the question "Has he/she at any time of his/her life suffered from attacks of asthma or wheezy breathing?" Smoking status of the participants was categorised as current, past and never-smokers. A current smoker was defined as smoking status within last four weeks. Pack-years were calculated as the number of cigarettes smoked per day divided by 20 multiplied by the number of years of smoking.(1) Childhood and adulthood socioeconomic status were defined using Australian census data of Socio-Economic Indexes for Areas (SEIFA indexes).(2) We used the Index of Education and Occupation (IEO) variables that focused on the skills of the people required in different occupations. A high IEO score indicated that individuals who lived in that area had high qualifications and highly skilled jobs.

Additional statistical analysis

We included 1,335 participants in the ever exposure analysis, but the participants with missing or incomplete job history (n=80) were excluded in cumulative EU-years analysis (N=1,255). Furthermore, we compared our complete-case analysis with multiple imputation by imputing the missing confounding variables (Supplementary Table S3, S4, and S5). The missing data ranged from 3% for pack-years to 0.3% for smoking, asthma, and socioeconomic status. Multiple imputation method in two-stages was used as a sensitivity analysis. In the first stage, the missing values were imputed by using chained equations ("mi impute chained" command) for 20 imputations in stata. In the second phase, the logistic regression analyses were performed in the imputed model including the same confounding variables that were included in the main complete-case analyses. We also tested Spearman rank correlation matrix between the exposures and the co-exposures were adjusted due to the presence of correlation.

SUPPLEMENTARY RESULTS

The prevalence of occupational exposures to biological dust, mineral dust, gases/fumes, VGDF, all pesticides, herbicides, and insecticides are presented in Supplementary Table S2. The most common exposure was the combined measure to VDGF with 75% of participants having exposure at some point in their working life. Exposure to gases/fumes was also high at 71%, followed by biological dust (55%), mineral dust exposure (52%), and the all pesticides (15.8%).

Table S1: Comparisons of characteristics between responders and non-responders at of 2002-2008 follow-up study

Study characteristics	**Laboratory attendees**	**Laboratory non-attendees**	**p-value***	**Completed Postal survey only**	**p-value ****
Sample size	**N=1,397**	**N=990**		**N=3,350**	
Sex, %			0.03		0.92
Men	684 (51.6)	509 (54.3)		1,574 (50.6)	
Women	651 (48.3)	417 (45.6)		1,558 (49.3)	
Smoking history					
Never, n (%)	586 (44.6)	323 (36.8)		1,366 (41.0)	
Past, n (%) Pack-years, median [IQR]	413 (29.6) 7.5[2-17.4]	259 (27.3) 11[2.3-22.5]	<0.000	1,037 (30.9) 8 [2-18.8]	0.71
Current, n (%) Pack-years, median [IQR]	392 (25.7) 21[9.5-30]	395 (35.8) 23.3[13.5-33.7]		933 (28.0) 19.5[10-29.4]	
Currently employed, n (%)	1,182 (87.0)	802 (84.4)	0.16	2,868 (85.9)	0.28
Chronic bronchitis	256 (12.4)	204 (14.8)	0.03	35 (4.8)	<0.000
Chronic cough	191 (8.7)	176 (11.2)	0.004	131 (3.2)	<0.000
Chronic phlegm	174 (6.6)	139 (7.9)	<0.000	84 (1.9)	<0.000
Dyspnoea	242 (12.2)	207 (14.6)	0.01	283 (7.2)	<0.000
Asthma	929 (39.8)	686 (44.2)	<0.000	710 (11.7)	<0.000
Child asthma	401 (15.2)	282 (15.3)	<0.000	112 (1.3)	<0.000

Definitions of abbreviations: SD, Standard Deviation; IQR, Interquartile Range;
†The estimate prevalences were calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the fifth decade follow-up survey
*compare lab attendees to non-attendees
** compared postal survey participants to lab attendees

Table S2: Adjusted prevalence of occupational exposures in the study population (n=1,335)

Study characteristics	Biological dust n(%)	Mineral dust n(%)	Gases/ fumes n(%)	VGDF n(%)	All pesticides n(%)	Herbicides n(%)	Insecticides n(%)
No exposure	579 (44.9)	628 (47.7)	375 (28.8)	322 (24.9)	1,109 (84.2)	1,148 (86.9)	1,151 (87.6)
Ever (low/high) exposure	756 (55.0)	707 (52.2)	960 (71.2)	1,013 (75.1)	226 (15.8)	187 (13.0)	184 (12.3)
Median [IQR] cumulative duration (years)	16.5 (6-30)	22 (8-48)	21.5 (9-38.5)	28 (12-76)	14.5 (4-28)	12 (6-27)	17.8 (8-34.5)

Table S3: Associations between ever exposures and cumulative EU-years and fixed AO -LLN using complete case analysis and multiple imputation

Exposures	**Fixed AO-LLN**	
	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**
Biological dust		
Not exposed	Ref.	Ref.
Exposed	**1.56 (1.00-2.45)**	**1.56 (1.00-2.45)**
Cumulative EU-years	1.03 (0.96-1.12)	1.05 (0.97-1.13)
Mineral dust		
Not exposed	Ref.	Ref.
Exposed	1.29(0.81-2.04)	1.29 (0.81-2.04)
Cumulative EU-years	1.03 (0.97-1.11)	1.05 (0.97-1.11)
Gases/fumes		
Not exposed	Ref.	Ref.
Exposed	1.47 (0.87-2.51)	1.48 (0.87-2.53)
Cumulative EU-years	1.02 (0.96-1.09)	1.02 (0.95-1.08)
VGDF		
Not exposed	Ref.	Ref.
Exposed	1.25 (0.72-2.15)	1.26 (0.73-2.17)
Cumulative EU-years	1.03 (0.97-1.08)	1.02 (0.97-1.08)
All pesticides		
Not exposed	Ref.	Ref.
Exposed	1.63 (0.91-3.07)	1.61 (0.91-2.87)
Cumulative EU-years	**1.13 (1.00-1.29)**	1.12 (0.99-1.24)
Herbicides		
Not exposed	Ref.	Ref.
Exposed	**1.95 (1.08-3.49)**	**1.92 (1.08-3.44)**
Cumulative EU-years	**1.15 (1.00-1.36)**	1.13 (0.98-1.31)
Insecticides		
Not exposed	Ref.	Ref.
Exposed	1.56 (0.84-2.90)	1.53 (0.83-2.84)
Cumulative EU-years	1.10 (0.96-1.26)	1.10 (0.97-1.24)

† Complete case-analysis; ± Multiple imputation

[†]Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights. The analyses with biological dust, mineral dust, gases/fumes, and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides, and insecticides were additionally adjusted for VGDF exposure. The bolded text identifies results reaching statistical significance ($p \leq 0.05$)

Table S4: Association between Ever Exposure and Fixed Airflow Obstruction, Chronic Bronchitis and Respiratory Symptoms using complete case analysis and multiple imputation

Exposures	Fixed AO-GOLD		Chronic bronchitis		Chronic cough		Chronic phlegm		Dyspnoea	
	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**
Biological dust										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	**1.58 (1.01-2.48)**	**1.57 (1.00-2.48)**	0.99 (0.67-1.48)	0.92 (0.61-1.38)	1.24 (0.83-1.84)	1.24 (0.83-1.85)	0.98 (0.66-1.46)	0.99 (0.66-1.47)	1.32 (0.95-1.85)	1.32 (0.94-1.86)
Mineral dust										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	1.29 (0.81-2.04)	1.30 (0.82-2.06)	1.10 (0.72-1.67)	1.06 (0.68-1.64)	**1.62 (1.06-2.48)**	**1.66 (1.09-2.51)**	**1.51 (1.00-2.30)**	**1.58 (1.03-2.40)**	**1.57 (1.10-2.23)**	**1.55 (1.08-2.21)**
Gases/fumes										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	1.50 (0.88-2.54)	1.49 (0.88-2.55)	0.91 (0.58-1.45)	0.88 (0.55-1.40)	1.25 (0.80-1.98)	1.27 (0.81-2.01)	1.20 (0.76-1.90)	1.23 (0.78-1.95)	1.31 (0.89-1.91)	1.31 (0.90-1.92)
VGDF										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	1.29 (0.73-2.17)	1.27 (0.74-2.19)	0.95 (0.58-1.55)	0.91 (0.55-1.50)	**1.69 (1.01-2.84)**	**1.72 (1.03-2.87)**	1.31 (0.80-2.17)	1.34 (0.82-2.22)	1.29 (0.86-1.93)	1.29 (0.86-1.92)
All pesticides										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	**1.74 (1.00-3.07)**	1.72 (0.99-3.04)	**1.81 (1.12-2.93)**	1.76 (0.99-3.14)	**1.77 (1.04-3.01)**	**1.86 (1.09-3.13)**	**2.06 (1.23-3.47)**	**2.18 (1.30-3.66)**	**1.95 (1.23-3.09)**	**2.01 (1.27-3.18)**
Herbicides										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	**2.09 (1.18-3.70)**	**2.06 (1.16-3.64)**	**1.81 (1.08-3.02)**	1.71 (0.96-3.05)	**1.79 (1.04-3.09)**	**1.89 (1.10-3.25)**	1.62 (0.93-2.83)	**1.74 (1.01-3.03)**	1.44 (0.89-2.34)	1.49 (0.92-2.42)
Insecticides										
Not exposed	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Exposed	1.70 (0.93-3.10)	1.66 (0.91-3.03)	**1.64 (1.00-2.72)**	1.51 (0.83-2.76)	**1.74 (1.00-3.05)**	**1.84 (1.05-3.18)**	1.62 (0.93-2.84)	**1.73 (1.00-3.00)**	1.58 (0.97-2.57)	**1.64 (1.01-2.68)**

Definitions of abbreviations: GOLD, Global Obstructive Lung Disease; AO, Airflow Obstruction; RR, Relative Risk; CI, Confidence Interval; VGDF, Vapour, Gases, Dust and Fumes

[†] Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights. The analyses with biological dust, mineral dust, gases/fumes, and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides, and insecticides were additionally adjusted for VGDF exposure.

The bolded text identifies results reaching statistical significance (p≤0.05)

Table S5: Association between Cumulative EU-years and Fixed Airflow Obstruction, Chronic Bronchitis and Respiratory Symptoms using complete-case analysis and multiple imputation

Cumulative exposures*	Fixed AO-GOLD		Chronic bronchitis		Chronic cough		Chronic phlegm		Dyspnoea	
	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**	Complete case **RR (95%CI)**	Imputed **RR (95%CI)**
Biological dust	1.05 (0.97-1.13)	1.05 (0.97-1.13)	1.06 (0.99-1.13)	1.00 (0.92-1.07)	**1.07 (1.00-1.15)**	1.05 (0.99-1.13)	1.01 (0.94-1.09)	0.98 (0.91-1.06)	0.99 (0.92-1.06)	0.99 (0.93-1.06)
Mineral dust	1.03 (0.97-1.10)	1.04 (0.97-1.11)	1.04 (0.98-1.11)	0.99 (0.92-1.06)	1.00 (0.93-1.07)	1.00 (0.94-1.08)	1.03 (0.96-1.10)	1.04 (0.98-1.12)	**1.05 (1.00-1.11)**	**1.06 (1.00-1.12)**
Gases/fumes	1.02 (0.96-1.09)	1.03 (0.96-1.10)	1.03 (0.97-1.09)	0.97 (0.91-1.04)	0.97 (0.91-1.04)	0.98 (0.91-1.04)	1.03 (0.98-1.10)	1.05 (0.99-1.12)	**1.05 (1.00-1.10)**	1.05 (0.99-1.11)
VGDF	1.02 (0.97-1.08)	1.03 (0.97-1.09)	**1.05 (1.00-1.10)**	0.99 (0.93-1.04)	1.03 (0.97-1.08)	1.03 (0.97-1.08)	1.03 (0.98-1.08)	1.04 (0.99-1.09)	1.02 (0.98-1.07)	1.03 (0.98-1.08)
All pesticides	**1.12 (1.00-1.25)**	**1.13 (1.01-1.26)**	**1.16 (1.10-1.30)**	1.07 (0.95-1.20)	**1.12 (1.00-1.28)**	**1.09 (1.00-1.22)**	**1.13 (1.00-1.30)**	1.03 (0.92-1.16)	0.94 (0.82-1.08)	0.97 (0.86-1.09)
Herbicides	**1.16 (1.00-1.32)**	**1.16 (1.00-1.32)**	**1.22 (1.05-1.41)**	1.08 (0.93-1.25)	1.12 (0.97-1.30)	1.09 (0.96-1.24)	1.10 (0.93-1.31)	1.00 (0.86-1.16)	0.91 (0.77-1.09)	0.97 (0.83-1.12)
Insecticides	1.10 (0.98-1.24)	1.12 (0.99-1.26)	**1.15 (1.02-1.29)**	1.06 (0.93-1.20)	1.06 (0.92-1.22)	1.05 (0.92-1.18)	1.13 (0.99-1.30)	1.05 (0.93-1.19)	0.94 (0.83-1.09)	0.97 (0.85-1.10)

Definitions of abbreviations: GOLD, Global Obstructive Lung Disease; AO, Airflow Obstruction; RR, Relative Risk; CI, Confidence Interval; VGDF, Vapour, Gases, Dust and Fumes

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weights. The analyses with biological dust, mineral dust, gases/fumes, and VGDF were additionally adjusted for all pesticides, whereas the analyses with all pesticides, herbicides, and insecticides were additionally adjusted for VGDF exposure.

The bolded text identifies results reaching statistical significance ($p \leq 0.05$)

Table S6: Correlations between the exposures as no, low, and high exposure (0/1/2) in the TAHS cohort

	Dusts				Pesticides		
Correlation	**Biological Dust**	**Mineral Dust**	**Gases and Fumes**	**VGDF**	**All pesticides**	**Herbicides**	**Insecticides**
Biological Dust		0.47	0.56	0.64	0.39	0.35	0.34
Mineral Dust			0.61	0.59	0.40	0.37	0.37
Gases and Fumes				0.90	0.28	0.25	0.24
VGDF					0.25	0.22	0.22
All pesticides						0.88	0.87
Herbicides							0.84

Table S7: Overview of number of workers with high exposure to all pesticides

ISCO-88 job description	**ISCO-88**	**n (%)**
High exposure to all pesticides (n=151)		
Farm-hands and labourers	9211	37 (24.5%)
Gardeners, horticultural and nursery growers	6113	31 (20.5%)
Market oriented crop and animal producer	6130	29 (19.2%)
Forestry labourers	9212	27 (17.8%)
Mixed crop growers	9322	27 (17.8%)

Table S8: Association between Ever (low and high) Exposure and Fixed Airflow Obstruction, Chronic Bronchitis and Respiratory Symptoms

Exposure	Fixed AO-GOLD			Chronic bronchitis			Chronic cough			Chronic phlegm			Dyspnoea		
	No 1,222	**Yes 113**	**RR (95%CI)** [†]	**No 1,075**	**Yes 246**	**RR (95%CI)**	**No 1,131**	**Yes 185**	**RR (95%CI)**	**No 1,146**	**Yes 171**	**RR (95%CI)**	**No 1,107**	**Yes 226**	**RR (95%CI)**
Biological dust															
No exposure	541	37	Ref.	484	87	Ref	516	53	Ref.	507	60	Ref.	504	75	Ref.
Low exposure	434	46	**1.63 (1.01-2.65)**	396	82	0.73 (0.46-1.14)	414	60	1.20 (0.78-1.84)	425	51	0.83 (0.53-1.29)	389	90	1.24 (0.86-1.78)
High exposure	247	30	1.47 (0.81-2.69)	196	77	1.59 (0.96-2.64)	227	44	1.35 (0.79-2.31)	226	44	1.35 (0.80-2.27)	214	62	**1.56 (1.00-2.48)**
Mineral dust															
No exposure	585	42	Ref.	522	98	Ref	564	54	Ref.	565	54	Ref.	544	84	Ref.
Low exposure	287	24	1.01 (0.57-1.79)	251	58	1.11 (0.67-1.83)	254	53	**2.08 (1.32-3.29)**	264	43	1.49 (0.92-2.41)	256	55	1.27 (0.84-1.93)
High exposure	350	47	1.60 (0.94-2.72)	303	90	1.08 (0.66-1.77)	339	50	1.13 (0.67-1.90)	329	58	1.54 (0.93-2.55)	307	88	**2.05 (1.33-3.15)**
Gases/fumes															
No exposure	352	22	Ref.	314	57	Ref	336	32	Ref.	335	33	Ref.	327	48	Ref.
Low exposure	515	46	1.47 (0.83-2.58)	454	101	0.88 (0.54-1.44)	479	76	1.42 (0.88-2.28)	485	69	1.22 (0.75-1.98)	465	95	1.21 (0.81-1.82)
High exposure	355	45	1.53 (0.82-2.84)	308	88	0.97 (0.56-1.70)	342	49	0.95 (0.54-1.69)	338	53	1.16 (0.66-2.03)	315	84	1.55 (0.97-2.46)
VGDF															
No exposure	300	21	Ref.	273	45	Ref	294	22	Ref.	289	26	Ref.	281	41	Ref.
Low exposure	411	32	1.20 (0.65-2.22)	363	76	0.88 (0.51-1.52)	379	58	**1.90 (1.09-3.29)**	387	42	1.34 (0.78-2.32)	371	72	1.05 (0.67-1.63)
High exposure	511	60	1.31 (0.71-2.41)	440	125	1.03 (0.60-1.78)	484	77	1.48 (0.83-2.65)	482	77	1.29 (0.73-2.26)	455	114	**1.72 (1.08-2.75)**
All pesticides															
No exposure	1,024	85	Ref.	916	183	Ref	977	116	Ref.	977	116	Ref.	940	169	Ref.
Low exposure	68	7	0.92 (0.35-2.44)	58	17	1.61 (0.72-3.57)	62	13	1.95 (0.92-4.16)	59	15	**2.41 (1.11-5.17)**	55	20	**2.41 (1.27-4.56)**
High exposure	130	21	**1.78 (1.01-3.27)**	102	46	**1.82 (1.08-3.07)**	118	28	1.68 (0.92-3.09)	122	24	**1.81 (1.04-3.15)**	112	38	**1.75 (1.03-2.95)**
Herbicides															
No exposure	1,061	87	Ref.	947	191	Ref	1,011	121	Ref.	1,008	124	Ref.	966	182	Ref.
Low exposure	66	11	2.02 (0.95-4.28)	57	20	1.62 (0.76-3.44)	59	17	**2.37 (1.19-4.71)**	63	13	1.58 (0.74-3.34)	60	17	1.65 (0.86-3.10)
High exposure	95	15	**2.15 (1.05-4.42)**	72	35	**1.95 (1.03-3.72)**	87	19	1.35 (0.66-2.78)	87	18	1.68 (0.83-3.39)	81	28	1.29 (0.70-2.36)
Insecticides															
No exposure	1,060	91	Ref.	947	194	Ref	1,012	123	Ref.	1,009	125	Ref.	970	181	Ref.
Low exposure	34	2	0.65 (0.14-2.90)	28	8	1.07 (0.38-3.02)	28	8	2.48 (0.97-6.33)	30	6	1.77 (0.64-4.92)	26	10	1.91 (0.82-4.41)
High exposure	128	20	**2.02 (1.07-3.79)**	101	44	**1.83 (1.04-3.19)**	117	26	1.59 (0.87-2.90)	119	24	1.60 (0.87-2.90)	111	36	1.50 (0.88-2.54)

- Adjusted for sex, smoking, pack-years, adult and childhood socio economic status, adult and child asthma and sampling weight. Additionally, all pesticides was adjusted for the analysis with biological dust, mineral dust, gases/fumes, VGDF while VGDF was adjusted for all pesticides, herbicides and insecticides

REFERENCES

1. Matheson MC, Benke G, Raven J, *et al*. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. *Thorax* 2005: 60: 645–651.

2. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) Technical Paper. Canberra.:Commonwealth of Australia; 2011. ABS Catalogue no. 2033.0.55.001; 2011.

Chapter 6 Occupational exposure to solvents and metals are associated with fixed airflow obstruction

6.1 Chapter introduction

This chapter includes a published paper with additional data supplement that investigated the association between occupational exposure to solvents and metals and fixed AO as defined by post-BD spirometry using a general population based ALOHA plus JEM (190). This paper provides evidence for the first time that sex significantly modified the association between workplace exposure to chlorinated solvents and fixed AO. Women in my sample have increased the risk of fixed AO with increasing cumulative exposure-unit years to chlorinated solvents, despite women have fewer years of exposure than men have. In addition, I also found a significant association between ever exposure to metal and fixed AO and lung function.

I was the first author for this publication.

6.2 Research questions and aims

6.2.1 Research questions

1. What is the relationship between occupational exposure to solvents and metals and fixed AO as defined by post-BD spirometry and gas transfer factor?
2. Is the effect of occupational exposure to solvents and metals and fixed AO and lung function have been modified by sex, smoking, and asthma?

6.2.2 Aims

1. To investigate the relationship between occupational exposure to solvents and metals and fixed AO and fixed AO plus low $D_L$co.
2. To examine how sex, smoking, and asthma modified the associations of exposure to solvents and metals and fixed AO.

6.3 Publication

6.3.1 Main document and online data supplement

Alif S, Dharmage S, Benke G, Dennekamp M, Burgess J, Perret J, Lodge C, Morrison S, Johns D, Giles G, Gurrin L, Thomas P, Hopper J, Baker R, Thompson B, Feather I, Vermeulen R, Kromhout H, Walters H, Abramson M, Matheson M. Occupational exposures

to solvents and metals are associated with fixed airflow obstruction. *Scand J Work Environ Health* 2017 (In press)

Original article

Scand J Work Environ Health – online first. doi:10.5271/sjweh.3662

Occupational exposures to solvents and metals are associated with fixed airflow obstruction

by Sheikh M Alif, MPH,[1] Shyamali C Dharmage, PhD,[1, 2] Geza Benke, PhD,[3] Martine Dennekamp, PhD,[3, 4] John A Burgess, PhD,[1] Jennifer L Perret, PhD,[1, 5] Caroline J Lodge, PhD,[1] Stephen Morrison, PhD,[6] David P Johns, PhD,[7] Graham G Giles, PhD,[1, 2, 8] Lyle C Gurrin, PhD,[1, 2] Paul S Thomas, PhD,[9] John L Hopper, PhD,[1] Richard Wood-Baker, MRCP,[7] Bruce R Thompson, PhD,[10] Iain H Feather, FRACP,[11, 12] Roel Vermeulen, PhD,[13] Hans Kromhout, PhD,[13] E Haydn Walters, FRACP,[1, 3, 7] Michael J Abramson, PhD,[3] Melanie C Matheson, PhD [1, 2]

Alif SM, Dharmage SC, Benke G, Dennekamp M, Burgess JA, Perret JL, Lodge CL, Morrison S, Johns DP, Giles GG, Gurrin LC, Thomas PS, Hopper JL, Wood-Baker R, Thompson BR, Feather IH, Vermeulen R, Kromhout H, Walters EH, Abramson MJ, Matheson MC. Occupational exposures to solvents and metals are associated with fixed airflow obstruction. *Scand J Work Environ Health* – online first. doi:10.5271/sjweh.3662

Objectives This study investigated the associations between occupational exposures to solvents and metals and fixed airflow obstruction (AO) using post-bronchodilator spirometry.

Methods We included 1335 participants from the 2002–2008 follow-up of the Tasmanian Longitudinal Health Study. Ever-exposure and cumulative exposure-unit (EU) years were calculated using the ALOHA plus job exposure matrix (JEM). Fixed AO was defined as post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) <0.7 and FEV_1/FVC<lower limit of normal. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) was combined with FEV_1/FVC<0.7 to define fixed AO plus low D_{LCO}. Multinomial regressions were used to estimate associations adjusting for possible confounders.

Results Ever-exposure to metals was associated with fixed AO [relative risk (RR) 1.71, 95% CI 1.03–2.85] and fixed AO lower limit of normal (RR 1.67, 95% CI 1.00–2.78). Women had lower cumulative EU years to chlorinated solvents [mean 20.9, standard deviation (SD) 13.4] than men (mean 28.6, SD 36.9). However, the risk of developing fixed AO and fixed AO plus low D_{LCO} associated with each cumulative EU year of chlorinated solvents were higher among women than men (RR 1.08 versus 0.99, P-value for effect measure modification=0.006; RR 1.08 versus 1.00, P-value for effect measure modification=0.02).

Conclusions We have shown ever-exposure to metals and chlorinated solvents are important risk factors for fixed AO. The effects for solvents were strongest among women. Preventive strategies need to be followed to reduce these exposures at the workplace.

Key terms ALOHA; chlorinated solvent; chronic obstructive pulmonary disease; COPD; JEM; job exposure matrix.

1 Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Melbourne, Victoria, Australia.
2 Murdoch Children's Research Institute, Melbourne, Victoria, Australia.
3 Department of Epidemiology & Preventive Medicine, School of Public Health & Preventive Medicine, Monash University, Melbourne, Victoria, Australia.
4 Graduate Entry Medical School, University of Limerick, Limerick, Ireland.
5 Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, Victoria, Australia.
6 Department of Medicine, University of Queensland, Brisbane, Queensland, Australia.
7 School of Medicine, University of Tasmania, Hobart, Tasmania, Australia.
8 Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, Victoria, Australia.
9 Faculty of Medicine, University of New South Wales, Sydney, New South Wales, Australia.
10 Allergy Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, Victoria, Australia.
11 Gold Coast Hospital, Southport, Queensland, Australia
12 Bond University, Robina, Queensland, Australia.
13 Environmental Epidemiology Division, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands.

Correspondence to: Professor Shyamali C Dharmage, Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Level 3, 207 Bouverie St, Carlton 3010, Australia. [E-mail: s.dharmage@unimelb.edu.au]

A number of studies have identified that exposures to solvents (1–4) and metals (5) can influence respiratory symptoms. However, only a few have investigated these exposures in relation to fixed airflow obstruction (AO) that is used to define chronic obstructive pulmonary disease (COPD) in epidemiological literature (6, 7).

Solvents are routinely used in industry and are present in products such as fuels, paints, printing, degreasing metal parts, and cleaning products (8, 9). Solvents can be further divided into "aromatic solvents" such as benzene and "chlorinated solvents" including trichloroethylene, and tetrachloroethylene (4, 9). On inhalation, solvents slowly damage the airways causing mucus hypersecretion and may subsequently lead to airflow obstruction (10). Population-based studies have suggested a link between occupational exposure to solvents and chronic nonspecific lung disease (1–3, 11) and reduced lung function using pre-bronchodilator (BD) spirometry (4, 11). However, their findings are limited by their reliance on self-reported exposure and the use of physician's diagnosis to define chronic nonspecific lung disease. The Dutch Life Lines Cohort Study found an association between chlorinated solvents and chronic mucus hypersecretion in participants without AO (7), but no association between chlorinated solvents and lower lung function and AO (6). Limitations of these studies included the use of pre-BD to define AO when the recommended criterion is post-BD (12) and the use of current job rather than a complete job history which allows assessment of cumulative exposure (13).

Metals are also commonly used in a variety of industrial processes (14) and, via the manipulation of metal products, metal form aerosols can be inhaled (15). Population-based studies have suggested an association between occupational exposure to metals and chronic nonspecific lung disease (1, 7). Only two population-based studies have assessed the relationship between metals exposure and AO defined using lung function measurements, and neither found a significant association (4, 7). However, these studies were again limited by the use of pre-BD spirometry to define AO.

We investigated the associations between exposures to solvents and metals and fixed AO defined by post-BD spirometry and used a general population-based job exposure matrix (JEM) to calculate ever-exposure and cumulative exposure-unit (EU) years.

Methods

Data collection

Our study included participants from the most recent laboratory phase of the Tasmanian Longitudinal Health Study (TAHS) for which the methodology has been reported previously (16). In brief, the TAHS began in 1968 when 8583 Tasmanian children born in 1961 and attending school in Tasmania were enrolled by their parents who completed a respiratory health questionnaire for the child, who then underwent clinical examinations and lung function measurements. Data for the current analysis were collected at the follow-up survey started in 2002. The follow-up began with tracing 7562 (88.1%) of the original 1968 cohort to an address and achieving a response of 5729 (78.4%) to a postal survey (16). A subgroup of these respondents, selected on the basis of their participation in previous follow-ups, and an enriched sample with a history of asthma and chronic bronchitis were invited to participate in a detailed laboratory study between 2005 and 2008. Of the 2387 individuals invited, 1397 (58.6%) attended the laboratory and completed lung-function testing, 354 (14.8%) completed a telephone questionnaire including lifetime work history calendar but did not attended the laboratory to complete lung-function testing and remaining 636 (26.7%) withdrew. At the laboratory visit, participants completed a detailed interviewer-administered respiratory health questionnaire, completed a lifetime work history calendar, performed pre- and post-BD lung-function tests, skin-prick testing, lung volumes, and diffusing capacity test.

Lung-function testing

Pre and post-BD lung function were measured using the Easyone Pro® ultrasonic spirometer (ndd, Medizintechnik, AG, Switzerland). Participants were asked not to smoke for 4–6 hours before testing. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) joint statement (17) and the highest value for FEV_1 and FVC was recorded from three acceptable and repeatable tests. Spirometry was repeated 10–15 minutes after short-acting bronchodilator (200 µg salbutamol) administered via a spacer.

Single breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) was measured according to international guidelines and adjusted to a standard haemoglobin concentration of 14.6 g/dL in men and 13.4 g/dL in women and corrected for the presence of carboxyhemoglobin (18). The average of two acceptable tests that agreed to within 10% was recorded. Predicted values of D_{LCO} were calculated using the prediction equations of Thompson and colleagues (19).

Lung-function definitions

Fixed AO was defined in two ways: first, according to the Global Initiative for Chronic Obstructive Lung Dis-

ease (GOLD) fixed cut-off criterion ($FEV_1/FVC<0.7$) (20) and second using $FEV_1/FVC<$lower limit of normal (LLN) as based on the Global Lung Initiative (GLI) 2012 reference equations (21).

Fixed AO plus low D_{LCO} was defined by $FEV_1/FVC<0.7$ and D_{LCO} <80% of predicted value (22).

Occupational exposures

Occupational exposure were classified based on a full job history that was completed during the laboratory visit or telephone interview. Participants were asked to list all the jobs held over their lifetime. We collected data including job title, industry type, company name, the year when job started and ended from 1599 participants. In this analysis, we included 1335 participants those have both work history calendar and completed lung-function testing at the 2002–2008 follow-up. The jobs reported in the calendars were coded according to the International Standard Classification of Occupations (ISCO-88) four- digit classification (23). These codes were then used to assign occupational exposures to solvents (three categories: aromatic solvents, chlorinated solvents, and other solvents) and metals using the ALOHA plus JEM (6, 24). The JEM classified subjects based on job code into no, low and high exposure.

Ever-exposure. We combined low and high exposure categories because the small number of participants in the high-exposed group limited the statistical analysis and assigned people as "ever exposure", if they had occupational exposure for any job over their working life (25).

Cumulative EU years. We estimated this by the number of years worked in a given job multiplied by the exposure intensity for the given job and summed for each individual and each exposure across all jobs performed. To allow for the combination of low and high exposure categories, years of exposure was weighted by four for high exposure and one by low exposure to calculate cumulative EU years (24).

Statistical methods

All the statistical analyses were performed using Stata 13.1 (Stata Corporation, College Station, TX, USA) statistical package. Multinomial logistic and linear regression models were used to analyzed the associations between occupational exposures and fixed AO (categorical) and lung-function measures (continuous). The lung function variables were normally distributed. The final multinomial model was adjusted for sex, smoking, pack-years, asthma in childhood and adulthood, and socioeconomic status in childhood and adulthood (see online supplementary material for details, www.sjweh.fi/index.php?page=data-repository). Sampling weights were derived by calculating the inverse probability of selection for the enriched sample of the 2002 to 2008 follow-up.

To investigate potential effect measure modification by sex, smoking, and current asthma, additive log risk model were compared with multiplicative risk ratio model using likelihood ratio test and Bayesian information criterion. We did not identify any effect measure modification between occupational exposure and smoking or current asthma status (results not shown). However, we did observe some effect measure modification with sex so results for the association between cumulative EU years and fixed AO are stratified by sex. We excluded the participants with missing or incomplete years started or ended (N=80) from the cumulative EU years analysis. All complete case analysis were additionally compared with multiple imputation for dealing with missing data (data not shown). A cut-off of $P<0.05$ was considered as statistically significant.

We examined the correlation between solvents and metals exposure with other exposures from the ALOHA plus JEM; vapors, gases, dust, and fumes (VGDF) and all pesticides exposures and did not see a strong correlation between any of these variables (data not shown). Additionally, in our final adjusted regression model, we included VGDF, and pesticides exposures as an additional confounder to observe if they changed the effect estimates. As the addition of these variables into the models did not change in the effect estimates by 10% or more (data not shown), we did not adjust our final models for these factors.

Results

The characteristics of the study population are presented in table 1. The mean age of participants was 44.8 years, and more than half (51.6%) were men. Men had a higher median smoking pack-years than women (table 1) and 25% men were current smokers, compared with 18% of women. A comparison of non-responders to different parts of the 2002 to 2008 follow-up study is shown in supplementary table S1. Briefly selected characteristics of the participants who did and did not attend laboratory were similar. Men were more likely to have had ever occupational exposure to solvents and metals than women (supplementary table S2).

Ever-exposure

Ever-exposure to chlorinated solvents was associated with an increased risk of fixed AO [relative risk (RR) 1.45, 95% CI 0.91–2.34] and fixed AO plus low D_{LCO}

(RR 2.19, 95% CI 0.98–4.91) with both approachings but not quite reaching statistical significance (table 2). Ever-exposure to metals was also significantly associated with an increased risk of fixed AO (RR 1.71, 95% CI 1.03–2.85) but the evidence for its association with of fixed AO plus low D_{LCO} was modest (RR 2.04, 95% CI 0.83–5.04).

We also investigated the association between ever-exposure to aromatic solvents, chlorinated solvents, other solvents, metals and lung function measures (FEV_1, FVC, FEV_1/FVC, and D_{LCO}) (supplementary table S3). We found significant association with lower FEV_1/FVC ratio for those with ever-exposure to metals (z-score FEV_1/FVC ratio; -0.17, 95%CI -0.33– -0.02), but we found no other significant associations (supplementary table S4).

We found the similar association between ever exposed to metals and pre-BD FEV_1/FVC<0.7 (RR 1.47, 95% CI 1.00–2.21) and FEV_1/FVC<LLN (RR 1.57, 95% CI 1.04–2.39) (supplementary table S5). Additionally, we found a significant association with other solvents (RR 1.39, 95% CI 1.00–1.93) and pre-BD airflow obstruction.

Effect measure modification and cumulative EU-years

We examined effect measure modification by sex, asthma status, and smoking status. We presented the associations between cumulative EU years and fixed AO and fixed AO plus low D_{LCO} stratified by sex in table 3. We found a significant effect measure modification between sex and cumulative EU years to chlorinated solvents on the risk of fixed AO-GOLD and fixed AO-LLN. We found women have less cumulative EU years to chlorinated solvents [mean 20.9, standard deviation (SD) 13.4] compared to men (mean 28.6, SD 36.9), but women have modified the association between cumulative EU years to chlorinated solvents and fixed AO-GOLD and fixed AO-LLN (RR 1.08, 95% CI 1.03–1.15) than men. Figures 1 and 2 displays the predicted probabilities of fixed AO that were computed using the estimates from the multivariate regression models. In this model, women with increasing chlorinated solvent EU years had a significantly increased risk of fixed AO. However, for men, we did not observe any such relationship. We observed a similar effect measure modification by sex for fixed AO plus low D_{LCO} (P-value for effect measure modification=0.02, figure 3).

Table 1. Study characteristics stratified by sex. [SD=standard deviation; IQR=interquartile range; GOLD=global initiative for chronic obstructive lung disease; LLN=lower limit of normal; D_{LCO}diffusing capacity of the lung for carbon monoxide.]

Study characteristics	Total (N=1335)						Men (N=684)				Women (N=651)				P-value
	N	%	Mean	SD	Pack-years		N	%	Pack-years		N	%	Pack-years		
					Median	IQR			Median	IQR			Median	IQR	
Age			44.8	0.8											0.01
Never smokers	566	45.2					292	44.4			274	46.3			
Past smokers	395	29.7			7.7	2–17.3	189	28.4	9.8	2.1–19	205	30.9	5.5	1.5–15	0.47
Current smokers	370	21			25.0	22.4–27.9	202	25	25	13.8–35	168	18	18	7.8–27	
Fixed AO-GOLD	113	6.0					70	7.2			43	4.8			0.01
Fixed AO-LLN	112	6.0					69	7.1			43	4.8			0.02
Fixed AO plus low D_{LCO}	35	1.7					19	1.9			16	1.5			0.76
Adult asthma	649	28.9					313	26.0			336	32.1			0.03
Child asthma	382	15.3					221	17.2			161	13.3			0.01

Table 2. Associations between ever-exposures, fixed airflow obstruction (AO) and fixed AO plus low diffusing capacity of the lung for carbon monoxide (D_{LCO}). [GOLD=global initiative for chronic obstructive lung disease; LLN=lower limit of normal; RR=relative risk.]

Exposure	Fixed AO-GOLD				Fixed AO-LLN				Fixed AO plus low D_{LCO}			
	No (N=1222)	Yes (N=113)	RR [a]	95% CI	No (N=1223)	Yes (N=112)	RR	95% CI	No (N=1164)	Yes (N=35)	RR	95% CI
Aromatic solvents												
Not exposed	873	70	Ref.		873	70	Ref.		827	24	Ref.	
Exposed	349	43	1.21	0.76–1.93	350	42	1.18	0.74–1.88	338	11	0.91	0.39–2.12
Chlorinated solvents												
Not exposed	964	78	Ref.		964	78	Ref.		914	23	Ref.	
Exposed	258	35	1.45	0.91–2.34	259	34	1.40	0.87–2.28	251	12	2.19	0.98–4.91
Other solvents												
Not exposed	749	58	Ref.		749	58	Ref.		710	19	Ref.	
Exposed	473	55	1.34	0.89–2.06	474	54	1.32	0.87–2.02	455	16	1.24	0.60–2.57
Metals												
Not exposed	948	72	Ref.		948	72	Ref.		898	22	Ref.	
Exposed	274	41	1.71	1.03–2.85	275	40	1.67	1.00–2.78	267	13	2.04	0.83–5.04

[a] Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma .

We did not observe that sex modifed the effect of other exposures or any effect modification by sex, smoking or asthma status for exposures to either solvents or metals and fixed AO. Sex did not modify any associations between any of the solvents or metals and AO when defined using pre-BD lung function (data not shown).

Discussion

Our study is the first to assess occupational exposures to solvents and metals examining both ever-exposure and cumulative EU years in this cohort. The major new finding is that increasing cumulative EU years to chlorinated solvents is significantly associated with increased risks of fixed AO for women but not men although mean cumulative EU years to chlorinated solvents was less among women. The observed associations with fixed AO were restricted to the cumulative EU years and not ever being exposed to aromatic, chlorinated, and other solvents. However, we did find that ever-exposure to metals was associated with fixed AO and a lower FEV_1/FVC ratio, but no association was observed with cumulative EU-years to metals.

To our knowledge, ours is the first study to show

Table 3. The association between cumulative exposure-unit (EU) years and fixed airflow obstruction (AO) and fixed AO plus low diffusing capacity of the lung for carbon monoxide (D_{LCO}). stratified by sex and adjusted for smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma. [GOLD=global initiative for chronic obstructive lung disease; LLN=lower limit of normal; RR=relative risk; SD=standard deviation.]

Exposure	Women					Men					P-value [a]
	N	Cumulative EU years		RR	95% CI	N	Cumulative EU years		RR	95% CI	
		Mean	SD				Mean	SD			
Aromatic solvents											
Fixed-AO-GOLD											
No	559	7.1	6.9	Ref		589	17.4	16.6	Ref		
Yes	39	38.3	57.1	1.02	0.98–1.07	68	13.4	11.2	0.99	0.97–1.01	0.17
Fixed-AO-LLN											
No	559	7.1	6.9	Ref		590	17.5	16.6	Ref		
Yes	39	38.3	57.0	1.03	0.99–1.07	67	12.7	10.5	0.99	0.97–1.01	0.14
Fixed AO + low D_{LCO}											
No	514	6.6	6.1	Ref		579	17.1	16.5	Ref		
Yes	14	38.3	57.0	1.05	0.98–1.14	18	17.5	10.9	0.99	0.95–1.03	0.05
Chlorinated solvents											
Fixed-AO-GOLD											
No	559	8.1	6.7	Ref		589	40.9	40.4	Ref		
Yes	39	20.9	13.4	1.08	1.03–1.15	68	28.6	36.9	0.99	0.98–1.00	0.006
Fixed-AO-LLN											
No	559	8.1	6.7	Ref		590	40.7	40.4	Ref		
Yes	39	20.9	13.4	1.08	1.03–1.15	67	29.3	37.4	0.99	0.98–1.00	0.006
Fixed AO + low D_{LCO}											
No	514	8.8	8.2	Ref		579	38.4	39.5	Ref		
Yes	14	23.7	5.3	1.08	1.01–1.17	18	47.3	47.7	1.00	0.99–1.02	0.02
Other solvents											
Fixed-AO-GOLD											
No	559	16.5	17.2	Ref		589	17.8	18.0	Ref		
Yes	39	19.1	19.9	1.01	0.99–1.03	68	12.5	10.0	0.99	0.97–1.01	0.17
Fixed-AO-LLN											
No	559	16.6	17.2	Ref		590	18.1	18.4	Ref		
Yes	39	18.9	19.2	1.01	0.99–1.03	67	11.6	9.2	0.98	0.96–1.00	0.12
Fixed AO + low D_{LCO}											
No	514	17.0	17.6	Ref		579	17.5	17.9	Ref		
Yes	14	21.0	27.3	1.02	0.99–1.04	18	17.6	10.1	0.99	0.96–1.02	0.27
Metals											
Fixed-AO-GOLD											
No	559	9.3	11.5	Ref		589	34.4	38.3	Ref		
Yes	39	27.0	22.5	1.05	0.98–1.12	68	24.1	33.4	0.99	0.99–1.00	0.17
Fixed-AO-LLN											
No	559	9.3	11.5	Ref		590	34.3	38.3	Ref		
Yes	39	27.0	22.5	1.05	0.98–1.13	67	24.4	33.8	0.99	0.99–1.00	0.17
Fixed AO + low D_{LCO}											
No	514	12.1	14.3	Ref		579	32.1	37.1	Ref		
Yes	14	20.5	27.6	0.87	0.39–1.94	18	38.7	46.8	1.00	0.99–1.02	0.58

[a] Likelihood ratio P-value for risk ratio modification between cumulative EU-years and sex.

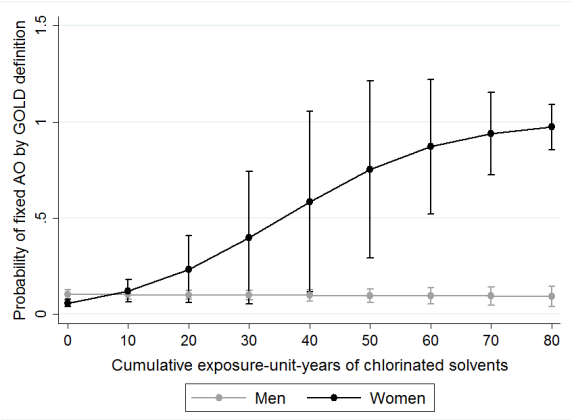


Figure 1. The associations between years of chlorinated solvents exposure and probability of fixed AO-GOLD, stratified by sex. Circles represent the probability of the outcome (fixed AO), and the bars represent the 95% confidence interval of that probability.

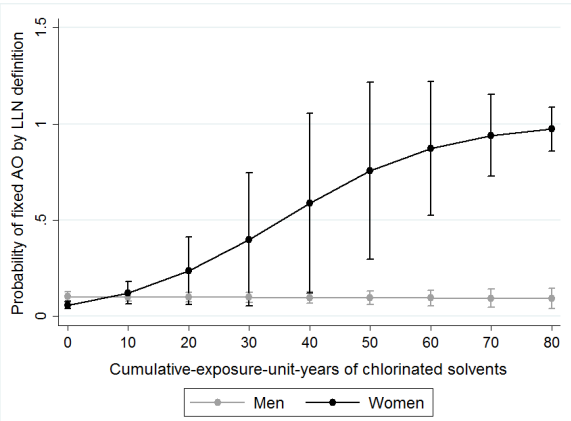


Figure 2. The association between years of chlorinated solvents exposure and probability of fixed AO-LLN, stratified by sex. Circles represent the probability of the outcome (fixed AO), and the bars represent the 95% confidence interval of that probability.

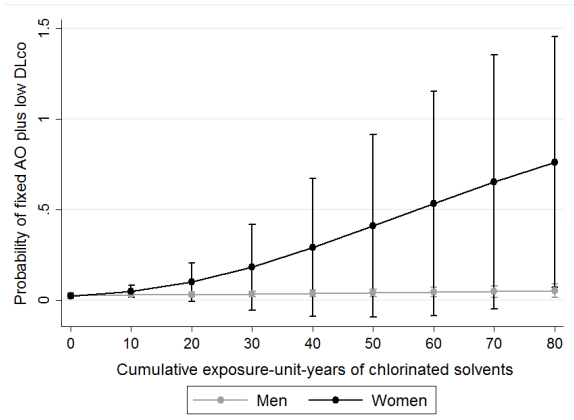


Figure 3. The association between years of chlorinated solvents exposure and probability of fixed AO plus low DLco, stratified by sex. Circles represent the probability of the outcome (fixed AO plus low DLco), and the bars represent the 95% confidence interval of that probability.

that cumulative EU years to chlorinated solvents is associated with fixed AO and fixed AO plus low D_{LCO} in women. The only study that assessed the association between ever- (low or high) exposure to chlorinated solvents and AO was limited to pre-BD lung function measures, which do not allow for clarifying the fixed nature of the airflow obstruction (6). However, similar to the LifeLines Cohort Study, we did not find any association between chlorinated solvents and AO defined using pre-BD airflow obstruction (6) nor any an effect modification by sex.

The different job distribution between men and women in our study may be another reason for increased risk among women. In our study, women exposed to chlorinated solvents worked as dry cleaners, laundry pressers, sculptors, painters, decorators and commercial designers, chemist, hairdresser or beauticians and chemical laboratory science technicians, while men were mostly metal, rubber, plastic product assemblers, glass, ceramics painters, mechanical and electrical technicians, painters, and sheet metal workers. Exposure to specific types of chlorinated solvents has been associated with symptoms of cough and phlegm in female laundry employees and dry cleaners (26). One might speculate that the increased risk of airflow obstruction among women who had occupational exposure to chlorinated solvents in our study might be related to an increased number for women to work in jobs with exposure to chlorinated solvents such as in the dry-cleaning or painting or pharmaceuticals industries. However, we actually found the women in our study had a lower prevalence of exposure and had fewer years of cumulative exposure to chlorinated solvents than men had. This raises the possibilities that the observed association could be related to the different types of chlorinated solvents used in different jobs undertaken by men and women, or alternatively, a greater degree of susceptibility to chlorinated solvents in women.

A greater susceptibility for women to develop fixed AO from inhaling respiratory pollutants has been debated over past decades (27). Postulated mechanisms include more toxin being deposited per surface area of the lungs, impaired clearance of the toxin substance or a modified biological response to the inhaled toxin (27, 28). Evidence from studies of smoking has shown that women receive a greater dose of toxin for the same amount of inhaled smoke because of their smaller airway size (29). Toxins in the airways are metabolized via the cytochrome P450 pathway (27). The female sex hormone estrogen can influence this pathway by causing the up-regulation of the CYP1A1, CYP1A2, CYP2A6, CYP3A4, and CYP1B1 cytochromes (28, 30). The role of these enzymes in the toxin metabolism pathway leads to increased oxidation of inhalation leading to increased oxidative stress in the airways and greater risk of airflow

obstruction in women (28). A recent *in vivo* animal study in mice suggested that female mice were more susceptible to airway remodeling with narrowed airway lumens and thickened airway walls compared to men, which they hypothesized was due to a greater susceptibility to oxidative stress due to the presence of the female sex hormone, estrogen (31). Studies among humans conflict with one study by Matheson et al (24) that found an increased risk of airflow obstruction among women exposed to biological dust but no increased risk among men. In contrast, some previous studies have assessed occupational exposure among men and women separately and have not observed any differences by sex (32, 33). A possible reason for this difference could that the latter two studies used pre-BD spirometry, and their study participants were younger and therefore less likely to have developed fixed AO. Importantly, none of these studies investigated chlorinated solvents exposure, and it may be that the chemical structure of chlorinated solvents increases the risk among women but not men. Overall, our findings add to the limited body of evidence that supports women as being more susceptible to the adverse lung function effect from specific occupational exposures.

Along with fixed AO, we also found an increased risk of fixed AO plus low D_{LCO} with increasing cumulative EU years to chlorinated solvents. Coexistent low D_{LCO} indicates the presence of emphysema as a diagnosis of emphysema requires either radiological evidence on computed tomography scan or a reduced gas transfer factor in the presence of chronic airflow obstruction (22). Others have also shown that some other occupational exposures have been associated with pulmonary emphysema at autopsy (34) or detected by computed tomography imaging (35). To our knowledge, no previous study has assessed the association between chlorinated solvents and emphysema. One previous study that used this definition of asymptomatic emphysema (airflow obstruction plus low D_{LCO}) found women with biological dust exposure were at an increased risk of emphysema (24). However, as we combined the definition of fixed AO with low D_{LCO}, there is a chance that the participants with fixed AO may have influenced or contributed in the combination of the two outcomes rather than gas transfer factor itself.

Ever-exposure to metals was associated with lower level of FEV_1/FVC and a greater risk of fixed AO in our study, and this is consistent with previous studies that found an increased risk of respiratory symptoms (7) and lung function decline (5, 36, 37) with exposure to metals in welders. For steelworkers, cumulative respirable metal dust exposure may cause pulmonary surfactant impairment resulting in lung function decline and chronic respiratory diseases (5). Subjects exposed to metals in our study were mainly working in metal or steel industries such as motor vehicle mechanics and fitters, sheet metal worker, welders and flame cutters and agriculture or industrial machinery mechanics. Our observation of an association between ever-exposure to metals was similar to previous studies that found an association between any exposure (high or low) to metals with lung function and chronic lung disease (1, 4, 7). However, due to lack of lifetime work history calendar, previous studies were unable to assess cumulative exposure (1, 4, 7).

The major strengths of our study include the use of post-BD spirometry to define fixed AO, the availability of lifetime work histories for the participants' entire working life, the use of a general population -based ALOHA plus JEM and adjustment for important potential confounding factors collected prospectively over time. The lifetime work histories allowed us to calculate ever and cumulative EU years and reduces the chance of recall bias as the participant is asked to recall their entire work history not just jobs they may recall as having high exposure to a possible causative agent. The main limitations of our study include possible sources of information bias, including recall and misclassification bias, and selection bias such as non-response bias. There is the possibility of recall or "exposure suspicion" bias caused by the participant's selective recall of exposures. We have at least reduced the possibility of this type of bias using a JEM based on lifetime work history calendars that collected information on all jobs the participant has ever held irrespective of the possibility of exposure. JEM themselves may be affected by non-differential misclassification bias of the exposure due to the heterogeneity of exposure within a given job title or occupation, but, if present, such non-differential misclassification would be expected to underestimate the true effects of exposure. Furthermore, the interviewing staff and participants were blinded to the occupational exposure hypothesis reducing the possibility of information biases. The next possible type of bias in our study is selection or non-response bias or "healthy volunteer" bias, caused by the participants choosing to participate in the laboratory study. Participants who self-select to participate in a study have in general better health than those who do not. We cannot fully exclude this type of bias however we did adjust all analysis for factors found to differ between those who attended the laboratory and those who did not. Based on these limitations, we suggest that our results should be viewed as hypothesis-generating rather than proof that these exposures are causal and replication in another cohort is needed.

In conclusion, our study has shown that cumulative EU years to chlorinated solvents is associated with increased risk of post-BD fixed AO among women but not men. We have also shown that this association is not due to greater exposure of women and suggest that this

may be due to their greater susceptibility. We also found that ever-exposure to metals was associated with fixed AO. Our study emphasizes the need to utilize post-BD spirometry to define fixed AO which allows adequate consideration of asthma, especially for a middle-aged population. Our findings highlight the need to reduce workplace exposure to solvents and metals by eliminating the source of exposure origin, improving adherence to use of recommended protective equipment, and workplace monitoring of exposure levels could be implemented. Preventive measures and exposure control strategies could be linked to periodic workplace risk assessment of the exposure in the relevant industries. By enhanced follow-up to and use of protective equipment, the burden of fixed AO caused by occupational exposures has the potential to be substantially reduced.

Acknowledgements

We acknowledge the Tasmanian Longitudinal Health Study (TAHS) participants and previous investigators. We thank Professor Mark Jenkins, PhD, Centre Director, Centre for Epidemiology and Biostatistics, School of Population and Global Health, The University of Melbourne, Victoria, who is a TAHS investigator but not a coauthor of this manuscript, for his assistance with obtaining funds and data collection. Furthermore, we acknowledge all the respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland, and New South Wales; the research interviewers and data entry operators; and the organizational roles of Ms. Cathryn Wharton and Dr. Desiree Mészáros.

This study was supported by the National Health and Medical Research Council (NHMRC) Australia project grant; Clifford Craig Medical Research Trust of Tasmania; Victorian, Queensland, and Tasmanian Asthma Foundations; and the Australian Lung Foundation. SCD is supported by the NHMRC, career development fellowship.

References

1. Heederik D, Kromhout H, Burema J, Biersteker K, Kromhout D. Occupational exposure and 25-year incidence rate of non-specific lung disease: the Zutphen Study. Int J Epidemiol. 1990;19:945–52. https://doi.org/10.1093/ije/19.4.945.

2. Heederik D, Pouwels H, Kromhout H, Kromhout D. Chronic non-specific lung disease and occupational exposures estimated by means of a job exposure matrix: the Zutphen Study. Int J Epidemiol. 1989;18:382–9. https://doi.org/10.1093/ije/18.2.382.

3. Post WK, Heederik D, Kromhout H, Kromhout D. Occupational exposures estimated by a population specific job exposure matrix and 25 year incidence rate of chronic nonspecific lung disease (CNSLD): the Zutphen Study. Eur Respir J. 1994;7:1048–55.

4. Le Moual N, Orlowski E, Schenker MB, Avignon M, Brochard P, Kauffmann F. Occupational exposures estimated by means of job exposure matrices in relation to lung function in the PAARC survey. Occup Environ Med. 1995;52:634–43. https://doi.org/10.1136/oem.52.10.634.

5. Hamzah NA, Mohd Tamrin SB, Ismail NH. Metal dust exposure and lung function deterioration among steel workers: an exposure-response relationship. Int J Occup Environ Health. 2016;22:224–32. https://doi.org/10.1080/10773525.2016.1207040.

6. de Jong K, Boezen H, Kromhout H, Vermeulen R, Postma D, Vonk J, et.al. Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study. Occup Environ Med. 2014;71:88–96. https://doi.org/10.1136/oemed-2013-101639.

7. Dijkstra AE, De Jong K, Boezen HM, Kromhout H, Vermeulen R, Groen HJM, et.al. Risk factors for chronic mucus hypersecretion in individuals with and without COPD: Influence of smoking and job exposure on CMH. Occup Environ Med. 2014;71:346–52. https://doi.org/10.1136/oemed-2013-101654.

8. Vizcaya D, Christensen KY, Lavoue J, Siemiatycki J. Risk of lung cancer associated with six types of chlorinated solvents: results from two case-control studies in Montreal, Canada. Occup Environ Med. 2013;70:81–5. https://doi.org/10.1136/oemed-2012-101155.

9. Neta G, Stewart PA, Rajaraman P, Hein MJ, Waters MA, Purdue MP, Samanic C, Coble JB, Linet MS, Inskip PD. Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults. Occup Environ Med. 2012;69:793–801. https://doi.org/10.1136/oemed-2012-100742.

10. Schenker MB, Jacobs JA. Respiratory effects of organic solvent exposure. Tuber Lung Dis. 1996;77:4–18. https://doi.org/10.1016/S0962-8479(96)90069-6.

11. Lebowitz MD. Occupational exposures in relation to symptomatology and lung function in a community population. Environ Res. 1977;14:59–67. https://doi.org/10.1016/0013-9351(77)90066-4.

12. Sterk P. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J. 2004;23:497–8. https://doi.org/10.1183/09031936.04.00017104.

13. Lilley RC, Cryer PC, Firth HM, Herbison GP, Feyer AM. Ascertainment of occupational histories in the working population: the occupational history calendar approach. Am J Ind Med. 2011;54:21–31. https://doi.org/10.1002/ajim.20903.

14. Aminian O, Zeinodin H, Sadeghniiat-Haghighi K, Izadi N. Respiratory Symptoms and Pulmonary Function Tests among Galvanized Workers Exposed To Zinc Oxide. J Res Health Sci.. 2015;15:159–62.

15. Koller MF, Pletscher C, Scholz SM, Schneuwly P. Metal working fluid exposure and diseases in Switzerland. Int J Occup Environ Health. 2016;22:193–200. https://doi.org/10.1080/10773525.2016.1200210.

16. Matheson MC, Abramson MJ, Allen K, Benke G, Burgess JA, Dowty JG, et al. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). Int J Epidemiol. 2017;46:407–8i.

17. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et.al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38. https://doi.org/10.1183/09031936.05.00034805.

18. Macintyre N, Crapo R, Viegi G, Johnson D, Van Der Grinten C, Brusasco V, et.al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–35. https://doi.org/10.1183/09031936.05.00034905.

19. T Thompson BR, Johns DP, Bailey M, Raven J, Walters EH, Abramson MJ. Prediction equations for single breath diffusing capacity (TlCO) in a middle aged caucasian population. Thorax. 2008;63:889–93. https://doi.org/10.1136/thx.2007.091959.

20. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et.al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Resp Crit Care Med. 2013;187:347–65. https://doi.org/10.1164/rccm.201204-0596PP.

21. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et.al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324–43. https://doi.org/10.1183/09031936.00080312.

22. Marsh SE, Travers J, Weatherall M, Williams MV, Aldington S, Shirtcliffe PM, et.al. Proportional classifications of COPD phenotypes. Thorax. 2008;63:761–7. https://doi.org/10.1136/thx.2007.089193.

23. Office IL. International Standard Classification of Occupations: ISCO-88. 1990 [cited 2014 February 22]. Available from: http://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm.

24. Matheson MC, Benke G, Raven J, Sim MR, Kromhout H, Vermeulen R, et.al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax. 2005; 60: 645–51. https://doi.org/10.1136/thx.2004.035170.

25. Alif SM, Dharmage SC, Benke G, Dennekamp M, Burgess JA, Perret JL, et al. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age. Thorax. 2017. Epub ahead of print. https://doi.org/10.1136/thoraxjnl-2016-209665.

26. LeVan TD, Koh WP, Lee HP, Koh D, Yu MC, London SJ. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese Health Study. Am J Epidemiol. 2006;163:1118–28. https://doi.org/10.1093/aje/kwj144.

27. Barnes PJ. Sex Differences in Chronic Obstructive Pulmonary Disease Mechanisms. Am J Respir Crit Care Med. 2016;193:813–14. https://doi.org/10.1164/rccm.201512-2379ED.

28. Sin DD, Cohen SB, Day A, Coxson H, Pare PD. Understanding the biological differences in susceptibility to chronic obstructive pulmonary disease between men and women. Proc Am Thorac Soc. 2007;4:671–4. https://doi.org/10.1513/pats.200706-082SD.

29. Chapman KR. Chronic obstructive pulmonary disease: are women more susceptible than men? Clin Chest Med. 2004;25:331–41. https://doi.org/10.1016/j.ccm.2004.01.003.

30. Hissink EM, Bogaards JJ, Freidig AP, Commandeur JN, Vermeulen NP, van Bladeren PJ. The use of in vitro metabolic parameters and physiologically based pharmacokinetic (PBPK) modeling to explore the risk assessment of trichloroethylene. Environ Toxicol Pharmacol. 2002;11:259–71. https://doi.org/10.1016/S1382-6689(02)00019-4.

31. Tam A, Churg A, Wright JL, Zhou S, Kirby M, Coxson HO, et.al. Sex Differences in Airway Remodeling in a Mouse Model of Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2016;193:825–34. https://doi.org/10.1164/rccm.201503-0487OC.

32. Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux PO, et.al. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary diseases in the swiss cohort study on air pollution and lung and heart diseases in adults. Am J Resp Crit Care Med. 2012;185:1292–300. https://doi.org/10.1164/rccm.201110-1917OC.

33. Sunyer J, Zock JP, Kromhout H, Esteban RG, Radon K, Jarvis D, et.al. Lung Function Decline, Chronic Bronchitis, and Occupational Exposures in Young Adults. Am J Resp Crit Care Med. 2005;172:1139–45. https://doi.org/10.1164/rccm.200504-648OC.

34. Hnizdo E, Sluis-Cremer GK, Abramowitz JA. Emphysema type in relation to silica dust exposure in South African gold miners. Am Rev Respir Dis. 1991;143:1241–7. https://doi.org/10.1164/ajrccm/143.6.1241.

35. Marchetti N, Garshick E, Kinney GL, McKenzie A, Stinson D, Lutz SM, et.al. Association between Occupational Exposure and Lung Function, Respiratory Symptoms, and High-Resolution Computed Tomography Imaging in COPDGene. Am J Resp Crit Care Med. 2014;190:756–62. https://doi.org/10.1164/rccm.201403-0493OC.

36. Ould-Kadi F, Nawrot TS, Hoet PH, Nemery B. Respiratory function and bronchial responsiveness among industrial workers exposed to different classes of occupational agents: a study from Algeria. J Occup Med Toxicol. 2007;2:11. https://doi.org/10.1186/1745-6673-2-11.

37. Rehfisch P, Anderson M, Berg P, Lampa E, Nordling Y, Svartengren M, et.al. Lung function and respiratory symptoms in hard metal workers exposed to cobalt. J Occup Environ Med. 2012;54:409–13. https://doi.org/10.1097/JOM.0b013e31824d2d7e.

Received for publication: 4 April 2017

Original article. Scand J Work Environ Health – online first

Occupational exposures to solvents and metals are associated with fixed airflow obstruction [1]

by Sheikh M Alif, MPH, Shyamali C Dharmage, PhD,[2] Geza Benke, PhD, Martine Dennekamp, PhD, John A Burgess, PhD, Jennifer L Perret, PhD, Caroline J Lodge, PhD, Stephen Morrison, PhD, David P Johns, PhD, Graham G Giles, PhD, Lyle C Gurrin, PhD, Paul S Thomas, PhD, John L Hopper, PhD, Richard Wood-Baker, MRCP, Bruce R Thompson, PhD, Iain H Feather, FRACP, Roel Vermeulen, PhD, Hans Kromhout, PhD, E Haydn Walters, FRACP, Michael J Abramson, PhD, Melanie C Matheson, PhD

1 *Supplementary material*

2 *Correspondence to: Professor Shyamali C Dharmage, Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne, Level 3, 207 Bouverie St, Carlton 3010, Australia. [E-mail: s.dharmage@unimelb.edu.au]*

METHODS

Quality and Calibration measures for lung function

All participant testing was performed in accredited lung function laboratories with trained staff and strictly followed ATS/ERS guidelines. Briefly, the accuracy of spirometer was checked regularly at the study site per the manufacturer's guideline with a 3L calibration syringe (15 mL volume calibration was used). The calibrated syringe was stored at the same temperature, maintained at the same humidity, kept away from sunlight and heat sources. Spirometers were also checked regularly to identify any leakages or mechanical errors.

Z-score conversion of lung function

We also calculated z-score values for post-bronchodilator FEV_1, FVC, and FEV_1/FVC from the Global Lung Initiative (GLI-2012) regression equations (1) which have been validated in an Australian population (2) and D_Lco from the reference equation by Thompson and colleagues (3). A z-score is the deviation from the mean predicted value, where 95% of the normally distributed population mean lies between –1.96 standard deviation (SD) to +1.96 SD. In other words, a positive z-score indicates the data point is above the population mean whereas a negative z-score indicates the data point is below the population mean. For example, if the z-score of the FEV_1 = -1.0, that signifies that the FEV_1 is less than the mean of the reference population (4). We also used pre-BD lung function to define airflow obstruction (AO) and compare the effect estimates observed with fixed nature of AO.

Definitions of confounding variables

Current asthma was defined by an affirmative response to the question "Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing?" and having the last attack of asthma within last 12 months. Childhood asthma was defined as asthma reported at age 7 and 13 by an affirmative response by the parents to the question "Has he/she at any time of his/her life suffered from attacks of asthma or wheezy breathing?" Smoking status of the participants was categorized as current, past and never-smokers. Current smoker was defined as smoking status within last four weeks. Pack-years were calculated as the number of cigarettes smoked per day divided by 20 multiplied by the number of years of smoking (5). Childhood and adulthood socioeconomic status were defined using Australian census data of Socio-Economic Indexes for Areas (SEIFA indexes) (6). We used

the Index of Education and Occupation (IEO) variables that focused on the skills of the people required in different occupations. A high IEO score indicated that individuals who lived in that area had high qualifications and highly skilled jobs.

RESULTS

A comparison of non-responders to different parts of the 2002 to 2008 follow-up study is shown in Supplementary material (Supplementary Table S1). We had a higher proportion of men in our "laboratory invitees but non-attenders" group, and our "laboratory invitees but non-attenders" were also more likely to be current and heavier smokers. Current employment status (employed or not) was not significantly different between the groups. Overall, 29.4% were exposed to aromatic solvents, 23.6% exposed to metals, 21.9% exposed to chlorinated solvents and 39.6% of participants were exposed to other solvents. Men were more likely to have had any exposure and to have had greater cumulative-EU-years to both solvents and metals than women (Supplementary Table S2).

Supplementary Table S1*:* Comparisons of characteristics between responders and non-responders at of 2002 to 2008 follow-up study

Study characteristics	Laboratory attendees	Laboratory non-attendees	p-value*	Completed Postal survey only	p-value **
Sample size	**N=1,397**	**N=990**		**N=3,350**	
Sex, %			0.03		0.92
Men	684 (51.6)	509 (54.3)		1,574 (50.6)	
Women	651 (48.3)	417 (45.6)		1,558 (49.3)	
Smoking history					
Never, n (%)	586 (44.6)	323 (36.8)		1,366 (41.0)	
Past, n (%)	413 (29.6)	259 (27.3)		1,037 (30.9)	
Pack-years, median[IQR]	7.5[2-17.4]	11[2.3-22.5]	<0.001	8 [2-18.8]	0.71
Current, n (%)	392 (25.7)	395 (35.8)		933 (28.0)	
Pack-years, median[IQR]	21[9.5-30]	23.3[13.5-33.7]		19.5[10-29.4]	
Currently employed, n (%)	1,182 (87.0)	802 (84.4)	0.16	2,868 (85.9)	0.28
Ever asthma	929 (39.8)	686 (44.2)	<0.001	710 (11.7)	<0.001
Child asthma	401 (15.2)	282 (15.3)	<0.001	112 (1.3)	<0.001

Definitions of abbreviations: SD, Standard Deviation; IQR, Interquartile Range;
† The estimate prevalences were calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the 2002 to 2008 follow-up survey
* comparing laboratory attendees to non-attendees
** compared postal survey participants to laboratory attendees

Supplementary Table S2: Descriptions of occupational exposures

Exposures	Both (n=1335)				Men (n=684)				Women (n=651)			
Aromatic solvents	**n**	**%**	**Median**	**IQR**	**n**	**%**	**Median**	**IQR**	**n**	**%**	**Median**	**IQR**
Not exposed	943	70.6			369	53.9			574	88.2		
Exposed	392	29.4			315	46.1			77	11.8		
Cumulative exposure			11	4.5-23			13	5-25.5			5	2-10
Chlorinated solvents												
Not exposed	1,042	78.1			446	65.2			596	91.6		
Exposed	293	21.9			238	34.8			55	8.5		
Cumulative exposure			18.5	6.5-45			23	8.5-56			8	2-13.5
Other solvents												
Not exposed	807	60.5			352	51.5			455	69.9		
Exposed	528	39.6			332	48.5			196	30.1		
Cumulative exposure			13	5-24.5			13	6-25			13	4-24.5
Metals												
Not exposed	1,020	76.4			388	56.7			632	97.1		
Exposed	315	23.6			296	43.3			19	2.9		
Cumulative exposure			17	6-42			18	6.5-46			5.5	1.5-26

Supplementary Table S3: Associations between ever exposures and lung functions (n=1335)

Exposures	N	Z-score FEV_1			Z-score FVC			Z-score FEV_1/FVC			Z-score D_LCO		
		β	95%CI	P-value	β	95%CI	P-value	β	95%CI	P-value	β	95%CI	P-value
Aromatic solvents													
Not exposed	942	Ref.			Ref.			Ref.			Ref.		
Exposed	392	0.05	-0.08 to 0.18	0.44	0.10	-0.02 to 0.22	0.09	-0.05	-0.17 to 0.08	0.47	0.02	-0.09 to 0.15	0.64
Chlorinated solvents													
Not exposed	1,041	Ref.			Ref.			Ref.			Ref.		
Exposed	293	0.02	-0.11 to 0.17	0.68	0.10	-0.02 to 0.23	0.11	-0.07	-0.21 to 0.06	0.29	-0.02	-0.15 to 0.11	0.77
Other solvents													
Not exposed	806	Ref.			Ref.			Ref.			Ref.		
Exposed	528	-0.06	-0.18 to 0.05	0.29	0.01	-0.09 to 0.12	0.79	-0.08	-0.20 to 0.03	0.12	0.02	-0.08 to 0.13	0.63
Metals													
Not exposed	1,019	Ref.			Ref.			Ref.			Ref.		
Exposed	315	-0.05	-0.20 to 0.09	0.48	0.08	-0.05 to 0.22	0.21	**-0.17**	**-0.33 to -0.02**	**0.01**	-0.04	-0.19 to 0.09	0.49

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma

Supplementary Table S4: Associations between cumulative-EU-years and lung functions (n=1201)

Exposures	Z-score FEV_1			Z-score FVC			Z-score FEV_1/FVC			Z-score D_LCO		
	β	95%CI	P-value	β	95%CI	P-value	β	95%CI	P-value	β	95%CI	P-value
Aromatic solvents	-0.01	-0.06 to 0.04	0.84	0.02	-0.02 to 0.06	0.42	-0.03	-0.08 to 0.02	0.23	-0.02	-0.06 to 0.03	0.47
Chlorinated solvents	-0.01	-0.03 to 0.02	0.64	-0.01	-0.02 to 0.02	0.93	0.0	-0.02 to 0.02	0.75	-0.02	-0.04 to 0.01	0.16
Other solvents	-0.01	-0.05 to 0.03	0.71	-0.01	-0.04 to 0.03	0.74	0.0	-0.04 to 0.04	0.86	-0.02	-0.05 to 0.02	0.39
Metals	-0.01	-0.03 to 0.02	0.52	-0.00	-0.02 to 0.02	0.73	0.0	-0.02 to 0.03	0.71	-0.01	-0.04 to 0.01	0.38

Supplementary Table S5: Associations between ever exposures, and airflow obstruction using pre-BD lung function measures

Exposure	Pre-BD $FEV_1/FVC<0.7$				Pre-BD $FEV_1/FVC<LLN$			
	No 1,138	**Yes 197**	**RR**	**95%CI**	**No 1,143**	**Yes 192**	**RR**	**95%CI**
Aromatic solvents								
Not exposed	816	127	Ref.		819	124	Ref.	
Exposed	322	70	1.21	0.84-1.74	324	68	1.23	0.85-1.78
Chlorinated solvents								
Not exposed	896	146	Ref.		899	143	Ref.	
Exposed	242	51	1.12	0.76-1.65	244	49	1.12	0.75-1.65
Other solvents								
Not exposed	705	102	Ref.		709	98	Ref.	
Exposed	433	95	**1.39**	**1.00-1.93**	434	94	**1.46**	**1.05-2.05**
Metals								
Not exposed	886	134	Ref.		890	130	Ref.	
Exposed	252	63	**1.47**	**1.00-2.21**	253	62	**1.57**	**1.04-2.39**

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma .

Supplementary Table S6: Association between cumulative EU-years, and airflow obstruction using pre-BD lung function measures

Cumulative EU-years	Pre-BD $FEV_1/FVC<0.7$			Pre-BD $FEV_1/FVC<LLN$		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Aromatic solvents	1.00	0.98-1.01	0.82	1.00	0.98-1.01	0.87
Chlorinated solvents	0.99	0.98-1.00	0.31	0.99	0.99-1.00	0.59
Other solvents	0.99	0.98-1.01	0.69	0.99	0.98-1.01	0.80
Metals	0.99	0.98-1.00	0.29	0.99	0.98-1.00	0.58

† Adjusted for sex, smoking, pack-years, childhood and adulthood socioeconomic status, and childhood and adulthood asthma .

Supplementary Table S7: Associations between ever exposures, fixed airflow obstruction-GOLD and fixed airflow obstruction-LLN stratified by sex

Exposure	Fixed AO -GOLD								Fixed AO -LLN							
	Men				Women				Men				Women			
	No 614	Yes 70	RR	95%CI	No 608	Yes 43	RR	95%CI	No 615	Yes 69	RR	95%CI	No 608	Yes 43	RR	95%CI
Aromatic solvents																
Not exposed	338	31	Ref.		535	39	Ref.		338	31	Ref.		535	39	Ref.	
Exposed	276	39	1.43	0.83-2.44	73	4	0.53	0.15-1.91	277	38	1.39	0.81-2.38	73	4	0.53	0.15-1.91
Chlorinated solvents																
Not exposed	405	41	Ref.		559	37	Ref.		405	41	Ref.		559	37	Ref.	
Exposed	209	29	1.29	0.75-2.22	49	6	2.03	0.78-5.30	210	28	1.25	0.72-2.15	49	6	2.03	0.78-5.30
Other solvents																
Not exposed	321	31	Ref.		428	27	Ref.		321	31	Ref.		428	27	Ref.	
Exposed	293	39	1.25	0.74-2.14	180	16	1.49	0.74-3.01	294	38	1.23	0.72-2.08	180	16	1.49	0.74-3.01
Metals																
Not exposed	356	32	Ref.		592	40	Ref.		356	32	Ref.		592	40	Ref.	
Exposed	258	38	1.63	0.95-2.80	16	3	1.88	0.40-8.95	259	37	1.58	0.92-2.73	16	3	1.88	0.40-8.95

Supplementary Table S8: Job distribution of number of participants exposed to chlorinated solvents

Job title description	ISCO-88	Number of participants
Women exposed to chlorinated solvents		
Hand-launderers and pressers	9133	12
Sculptors, painters and related artists	2452	11
Decorators and commercial designers	3471	9
Chemist	2113	9
Hairdresser or beauticians	5141	7
Chemical and physical science technicians	3111	5
Precision, handicraft, printing and related trades workers	7300	2
	Total	55
Men exposed to chlorinated solvents		
Metal-, rubber- and plastic-products assemblers	8284	46
Glass, ceramics and related decorative painters	7324	38
Mechanical engineering technicians	3115	32
Electrical and electronic equipment mechanics and fitters	7240	27
Sheet metal workers	7213	27
Painters, building structure cleaners and related trades workers	7140	25
Blacksmiths, tool-makers and related trades workers	7220	18
Wood treaters, cabinet-makers and related trades workers	7420	13
Metal finishing-, plating- and coating-machine operators	8223	12
Ships' engineers	3141	6
	Total	238

REFERENCES

1. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et.al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J 2012; 40: 1324-1343.

2. Hall GL, Thompson BR, Stanojevic S, Abramson MJ, Beasley R, Coates A, et al. The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. Respirology 2012; 17: 1150-1151.

3. Thompson BR, Johns DP, Bailey M, Raven J, Walters EH, Abramson MJ. Prediction equations for single breath diffusing capacity (TlCO) in a middle aged caucasian population. Thorax 2008; 63: 889-893.

4. Lambert A, Drummond MB, Wei C, Irvin C, Kaminsky D, McCormack M, et al. Diagnostic accuracy of FEV 1/forced vital capacity ratio z scores in asthmatic patients. J Allergy Clin Immunol 2015; 136: 649-653.

5. Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret JL, et al. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age. Thorax 2017 (In press).

6. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) Technical Paper. Canberra.:Commonwealth of Australia; 2011. ABS Catalogue no. 2033.0.55.001; 2011.

Chapter 7 Occupational exposures and lung function decline

7.1 Chapter abstract

People occupationally exposed to dusts, gases, fumes, and pesticides are at a greater risk of lung function decline and increased risk of COPD in their later life. Cross-sectional studies have shown an association between these occupational exposures and lower level of lung function. However, longitudinal analysis using a general population-based sample for the association between occupational exposures and lung function decline is very limited. Furthermore, occupational exposure to solvents, which has known respiratory health effects, have not been widely investigated in longitudinal analysis. The aim of this study was to investigate the association between occupational exposure and longitudinal lung function decline.

Decline in lung function between age 45 and 50 years was assessed using 767 participants from the Tasmanian Longitudinal Health Study. Lifetime work history calendars were recorded at age 45 years, and occupational exposure was assigned using the ALOHA plus JEM and defined as ever exposure and cumulative exposure-unit-years. I tested effect modification by sex, smoking and asthma status.

Ever exposure to aromatic solvents and metals were associated with a greater decline in FEV_1 (aromatic solvents -15.53mL/year [95%CI; -24.78, -6.28]; metals -11.31mL/year [-21.92, -0.69]) and FVC (aromatic solvents -14.06mL/year [-28.76, -0.65]; metals -17.54mL/year [-34.32, -0.76]). Cumulative exposure-unit-years to aromatic solvents were also associated with greater decline in FEV_1 and FVC. Women had lower cumulative exposure-unit-years to aromatic solvents than men (mean[SD] 9.6[15.5] vs 16.6[14.6]) but women had greater lung function decline than men. We also found an association between ever exposure to gases/fumes and mineral dust with greater decline in lung function.

In this longitudinal analysis, I found associations between different classes of occupational exposures and a greater lung function decline between the ages of 45 and 50 years. In particular, both aromatic solvents and metals exposure were associated with greater lung function decline. I also found women had a greater lung function decline compared to

men even with fewer years of exposure to aromatic solvents. This highlights the need for greater preventive strategies aimed at reducing exposure to solvents at the workplace.

7.2 Chapter introduction

Adult lung function decline is a normal feature of aging, but an excess decline during adulthood can result in COPD, and is a predictor of higher overall mortality and morbidity (4). Identification of modifiable risk factors for early lung function decline therefore has important broad health implications. However, the evidence on such factors is scarce due to a limited number of studies with repeated lung function measurements over time.

Occupational exposures, mainly VGDF (90, 166, 168, 169) and pesticides, (90) have been investigated as risk factors for lung function decline in previous studies. While some have observed these exposures to have a detrimental effect on lung function decline. others have contradicted these findings (84, 170). Two common exposures gaining increasing recognition as having an impact on lung function are solvents and metals exposures (24, 153). Cross-sectional studies have suggested that exposure to solvents (153, 154) and metals (154) are associated with lower levels of lung function but these studies have been unable to establish a temporal relationships.

A major limitation of some of the previous population-based studies of lung function decline have been the use of self-reported data on occupational exposure and/or current or most recent job to define occupational exposure, which is subject to information and selection bias (167-169). JEMs provide some protection from these types of bias because they are applied consistently to reported job title and do not rely on self-exposure assessment and therefore the use of lifetime WHC enables cumulative exposures to be calculated (54). However, few population-based studies have used JEMs to investigate the association between occupational exposures and lung function change, but none have investigated exposures to solvents and metals (84, 90, 165) using JEM. Another limitation is the lack of investigation into effect modification by sex given some studies have shown women having a higher susceptibility to occupational exposures (171, 172).

Given the discrepancies with and limitations of the occupational studies conducted to date, in this chapter, my aim was to investigate the association between occupational exposure and lung function decline using a general population-based cohort. I also investigated potential effect modification on the relationship by sex, asthma and smoking status.

7.3 Research questions and aims

7.3.1 Research questions

1. What is the association between occupational exposures and lung function decline?
2. Is the effect of occupational exposure and lung function decline have been modified by sex, smoking, and asthma?

7.3.2 Aims

1. To investigate the relationship between occupational exposures and lung function decline.
2. To examine the potential effect modification by sex, smoking, and asthma on these relationships.

7.4 Methods

7.4.1 Study design

The study consisted of participants from the 2002 to 2008 and 2010 to 2012 follow-up surveys of the TAHS for which methodology and previous results have been published elsewhere (29). Briefly, TAHS began in 1968 by recruiting essentially all 8583 school children born in 1961 (98.9% response rate) in Tasmania. In 2002 to 2008 follow-up, 7562 (88.1%) participants were traced to a residential address, and 5,729 (78.4%) responded to a postal survey. Starting in 2004 a subsample (n=2387) of these participants, selected on the basis of participation in previous follow-ups and enriched for participants with a history of asthma and bronchitis were invited to take part in a detailed clinical study. Of those 2004 clinical study participants invited, 1397 (58.6%) participated and 354 (14.8%) completed a telephone questionnaire only. In 2010, a new follow-up was conducted on the laboratory attendees from the 2004 clinical study participants. Of 1397 who were eligible, a small

number of participants had died or had withdrawn from the cohort (29). Therefore, of the remaining 1375 were re-invited, 840 (61.1%) took part in a full laboratory visit, 286 (20.8%) declined to participate and 249 (18.1%) could not be located. (Figure 7.1). In this analysis, I included 767 participants who completed lung function testing at both follow-ups and lifetime work history calendar during 2002 to 2008 follow-up study.

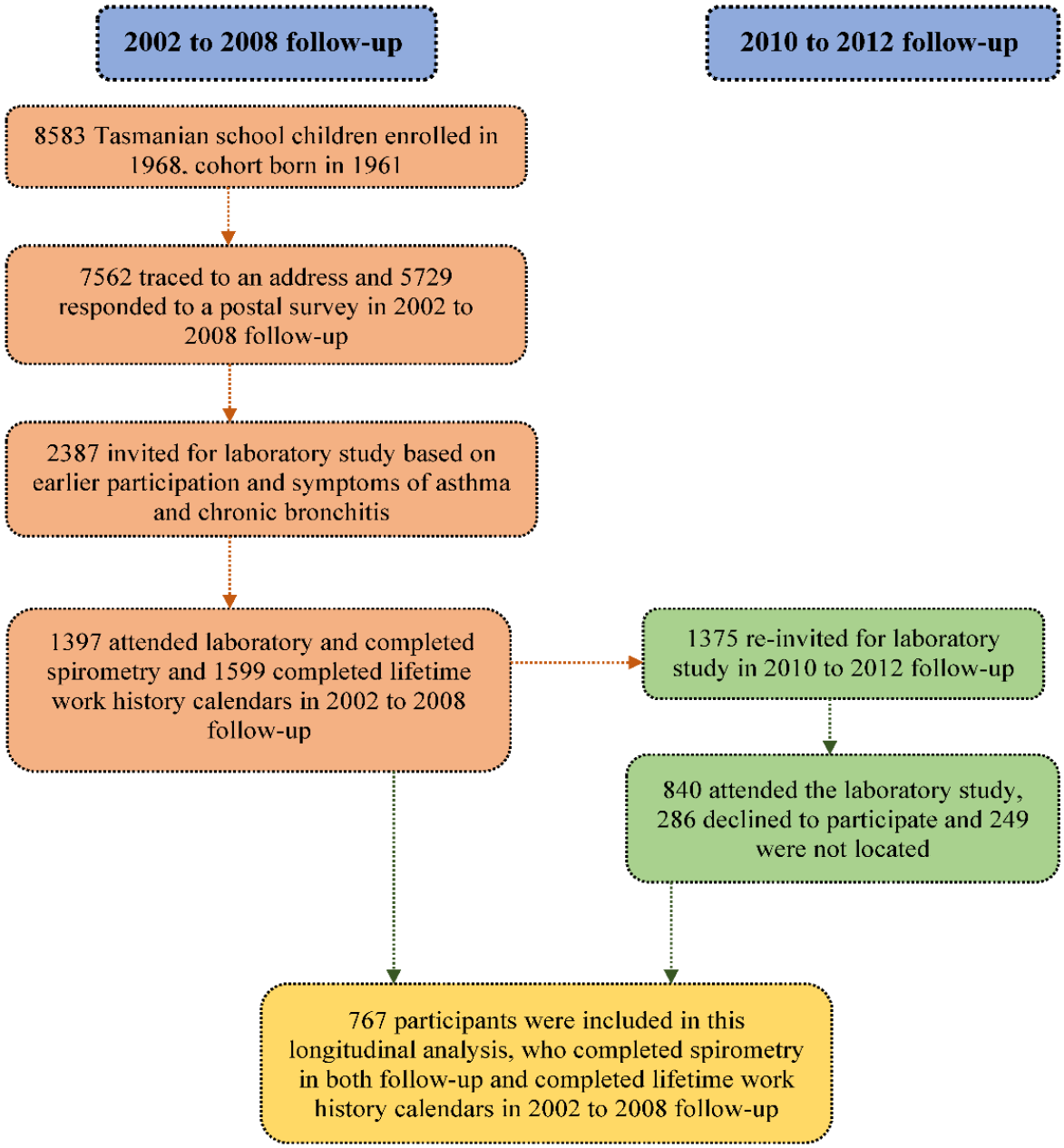


Figure 7.1 Flow chart illustrating study design in two follow-ups

7.4.2 Lung function measurements

Both pre-and post- BD spirometry was collected in first follow-up (2002 to 2008) but only pre-BD spirometry was conducted in 2010 to 2012 follow-up. Therefore, this analysis was able to investigate only the pre-BD lung function decline. During the follow-up, FEV_1 and FVC were measured using the EasyOne Pro® Ultrasonic Spirometer (ndd, Medizintechnik, AG, Switzerland) according to the American Thoracic Society (ATS) and European Respiratory Society (ERS) joint statement (40). Pre-BD lung function decline was calculated as FEV_1 (mL/year) (ΔFEV_1), FVC (mL/year) (ΔFVC) and FEV_1/FVC (%/year) ($\Delta FEV_1/FVC$) divided by the time interval (in years).

7.4.3 Occupational exposures

Occupational exposure was classified using the lifetime work history calendars that were collected from the participants from the 2002 to 2008 follow-up. Details of occupational exposure assessment were reported in the Chapter 4, section 4.4 in this thesis. I used general population-based JEM called the ALOHA plus JEM (85) and assigned exposures into biological dust, mineral dust, gases/fumes, VGDF, all pesticides, herbicides, insecticides, aromatic solvents, chlorinated solvents, other solvents and metals. In case participants had two different jobs at the same time, exposures of both jobs were averaged and allocated half of the exposure. I defined people as having ever exposure if they had exposure for any job over their working life. I also combined low and high exposure categories to define as ever exposure because of the small number of participants in the high exposure group limiting the statistical analysis. Cumulative exposure-unit (EU)-years were calculated by multiplying the number of years worked in a given job and exposure intensity squared for the given job (19).

7.4.4 Definitions of confounders

Having had asthma was defined by an affirmative response to the question "Have you ever had asthma?" Current asthma was based on self-reported symptoms in the morning, day-time and night-time or flare-ups in the last 12 months. Childhood asthma was defined as asthma reported at age 7 and 13 by an affirmative response by the parents to the question "Has he/she at any time of his/her life suffered from attacks of asthma or wheezy breathing?" Smoking status of the participants was categorised as current, past and never-smokers.

Current smoker was defined as smoking status within last four weeks. Pack-years were calculated as the number of cigarettes smoked per day divided by 20 multiplied by the number of years of smoking (19). Childhood and adulthood socioeconomic status were defined using Australian census data of Socio-Economic Indexes for Areas (SEIFA indexes) (186). I used the Index of Education and Occupation (IEO) variables that focused on the skills of the people required in different occupations. A high IEO score indicated that people who lived in that area had high qualifications and highly skilled jobs.

7.4.5 Statistical analyses

Stata 13.1 (Stata Corporation, College Station, Texas, USA) was used for all analysis. The association between occupational exposure and spirometric indices was investigated using multiple linear regression. The estimates were calculated using inverse-probability-of-inclusion weights to adjust for the enriched sample of the 2002 to 2008 follow-up. The regression models were adjusted for sex, height, smoking status, pack-years, childhood asthma, current asthma in both follow-up, and socioeconomic status in both childhood and adulthood (186).

Effect modification by sex, smoking, and asthma on the association between occupational exposure and lung function decline was also assessed. I compared the model with or without effect modification, and the p-value was reported using likelihood ratio test. I did not find any effect modification by smoking and asthma, but I did observe effect modification with sex, and therefore, the association between cumulative EU-years and lung function decline was further stratified by sex. A p-value<0.05 was considered as statistically significant.

The final models of biological dust, mineral dust, gases/fumes, and VGDF were additionally adjusted for pesticides, the models of pesticides, were adjusted for VGDF and models analysing solvents, and metals were additionally adjusted for both VGDF and pesticides due to the presence of correlation (Table E4). Furthermore, three categories of solvents (aromatic, chlorinated and other solvents) were included one by one as an additional confounder in the adjusted regression model with another solvents exposure (for example;

chlorinated and other solvents were added to the model with aromatic solvents) to observe the change in the effect estimates. As this model does not alter the effect estimated by 10% or more, additionally confounders were not included in the final model. Participants with missing work history calendar (n=44) were excluded in cumulative EU-years analysis.

7.5 Results

7.5.1 Population characteristics

Table 7.1 presents the characteristics of study participants. Virtually half of the 767 participants who took part in both the clinical follow-ups were men (49.97%). The average follow-up time was six years. Between the follow-up visits, the percentage of active smokers decreased from 20% to 15% (Table 1). The estimated mean lung function decline for all participants was -27.75 mL/year for FEV_1 (95% CI -31.32, -24.19), -33.37 mL/year for FVC (95% CI -39.02, -27.74), and -0.63 %/year for FEV_1/FVC ratio (95% CI -0.69, -0.56).

Table 7.1 Study characteristic and lung function

Study characteristics	**2002 to 2008 follow-up**	**2010 to 2012 follow-up**
Age, year (mean, SD)	44.84 (0.82)	49.61 (0.61)
Sex, n (%)		
Men	382 (49.97)	
Women	385 (50.0)	
Height, cm (mean, SD)	170.36 (8.67)	
Smoking history		
Never, n (%)	345 (47.07)	345 (46.21)
Past, n (%)	243 (32.68)	284 (38.92)
Pack-years, median [IQR]	6.3 [1.8-17.8]	6.3 [1.4-18]
Current, n (%)	179 (20.24)	138 (14.86)
Pack-years, median [IQR]	21 [7.5-30]	24.5 [12.6-33]
Pre-bronchodilator lung function (mean, SD)		
FEV_1, mean decline (mL/year, 95% CI)	-27.75 (-31.32, -24.19)	
FVC, mean decline (mL/year, 95% CI)	-33.37 (-39.02, -27.74)	
FEV_1/FVC, mean decline (%/year, 95% CI)	-0.63 (-0.69, -0.56)	
Current asthma, n (%)	203 (17.51)	177 (14.91)

7.5.2 Prevalence of occupational exposures

The prevalence of occupational exposures is presented in Table 7.2. The most common exposure was the combined measure to VDGF with 75% of participants having exposure at some point in their working life. Exposure to gases/fumes was also high at 71%, followed by biological dust (53%), mineral dust exposure (50%), aromatic solvents (29%) and metals (22%).

Table 7.2 Prevalence of occupational exposures

Exposures	Not exposed n (%)	Exposed n (%)	Cumulative EU- years (IQR)
Biological dust	350 (47.1)	417 (52.8)	16 (6-29.5)
Mineral dust	379 (49.9)	388 (50.1)	17.5 (6-44)
Gases/fumes	223 (29.4)	544 (70.5)	19 (8-33)
VGDF	193 (25.6)	574 (74.3)	25 (10.5-64)
Aromatic solvents	550 (71.5)	217 (28.5)	10.5(4.5-23)
Chlorinated solvents	616 (79.5)	151 (20.4)	19.5 (7.5-52)
Other solvents	471 (61.2)	296 (38.7)	14(5-26)
Metals	606 (78.1)	161 (21.8)	19 (6-48.5)
All pesticides	646 (86.0)	121 (13.9)	16 (6-31.5)
Herbicides	665 (87.9)	102 (12.0)	10 (4-24)
Insecticides	672 (89.0)	95 (10.9)	16 6-33.5)

7.5.3 Ever exposure to occupational exposures and lung function decline

Table 7.3 shows the association between ever exposure to dust, gases/fumes, solvents and metals and lung function decline. Those who were ever exposed to gases/fumes had a significant greater decline in FEV_1 of -11.7 mL/year (95%CI; -19.51, -3.9) compared to those not exposed to gases/fumes.

Ever exposure to aromatic solvents was associated with a greater decline in FEV_1 (-15.53 mL/year, 95%CI; -24.78, -6.28) and FVC (-14.06 mL/year, 95% CI; -28.76, -0.65) but not with FEV_1/FVC ratio. Ever exposure to metals was associated with a greater decline in FEV_1 (-11.31 mL/year, 95%CI; -21.92, -0.69) and FVC (-17.54 mL/year, 95% CI; -34.32, -0.76). Ever exposure to chlorinated solvents was associated with greater decline in FEV_1 (-11.56 mL/year, 95%CI; -21.54, -1.57) but not with FEV_1/FVC ratio and FVC. Ever exposure

to mineral dust (-0.17%/year, 95% CI; -0.32, -0.02), and gases/fumes (-0.20%/year, 95% CI; -0.36, -0.05) were associated with a greater decline in FEV_1/FVC ratio. No significant association were found for any forms of pesticides with any of the outcome (Table 7.4).

Table 7.3 Associations between ever exposures to dust and solvents and declines in lung function

Exposure	n	ΔFEV$_1$ (mL/year) β (95%CI) †	P	ΔFVC (mL/year) β (95%CI)	P	ΔFEV$_1$/FVC (%/year) β (95%CI)	P
Biological dust							
Not exposed Mean (SE)	350	-26.94 (2.89)		-26.24 (4.74)		-0.69 (0.05)	
Exposed Mean (SE)	417	-28.44 (2.29)		-39.36 (3.45)		-0.58 (0.04)	
Unadjusted mean (95% CI)		-1.49 (-8.65, 5.65)	0.68	**-13.11 (-24.40, -1.83)**	**0.02**	0.10 (-0.02, -0.23)	0.12
Adjusted mean (95% CI)		0.47 (-7.72, 8.68)	0.91	-9.3 (-22.23, 3.62)	0.16	0.05 (-0.09, 0.20)	0.49
Mineral dust							
Not exposed Mean (SE)	379	-25.37 (2.64)		-31.47 (3.61)		-0.64 (0.04)	
Exposed Mean (SE)	388	-30.08 (2.49)		-35.24 (4.44)		-0.62 (0.05)	
Unadjusted mean (95% CI)		-4.71 (-11.82, 2.41)	0.20	-3.76 (-15.04, 7.51)	0.51	0.02 (-0.12, 0.14)	0.82
Adjusted mean (95% CI)		-4.55 (-13.08, 3.96)	0.29	3.75 (-9.72, 17.22)	0.59	**-0.17 (-0.32, -0.02)**	**0.03**
Gases/fumes							
Not exposed Mean (SE)	223	-19.45 (3.71)		-26.02 (4.81)		-0.56 (0.06)	
Exposed Mean (SE)	544	-31.16 (2.04)		-36.39 (3.52)		-0.66 (0.04)	
Unadjusted mean (95% CI)		**-11.7 (-19.51, -3.9)**	**0.003**	-10.38 (-22.78, 2.02)	0.10	-0.09 (-0.23, 0.04)	0.19
Adjusted mean (95% CI)		**-11.43 (-20.0,-2.86)**	**0.009**	-4.96 (-18.55, 8.62)	0.47	**-0.20 (-0.36, -0.05)**	**0.09**
VGDF							
Not exposed Mean (SE)	193	-21.08 (3.89)		-24.9 (5.25)		-0.55 (0.06)	
Exposed Mean (SE)	574	-30.0 (2.03)		-36.22 (3.4)		-0.66 (0.03)	
Unadjusted mean (95% CI)		**-8.92 (-17.11,-0.73)**	**0.03**	-11.32 (-24.29, 1.65)	0.08	-0.11 (-0.26, 0.04)	0.16
Adjusted mean (95% CI)		-7.83 (-16.69, 1.02)	0.08	-5.75 (-19.76, 8.25)	0.42	**-0.22 (-0.38, -0.06)**	**0.07**
Aromatic solvents							
Not exposed Mean (SE)	550	-23.87 (2.04)		-29.08 (3.13)		-0.64 (0.04)	
Exposed Mean (SE)	217	-37.59 (3.7)		-44.26 (6.27)		-0.62 (0.06)	
Unadjusted mean (95% CI)		**-13.72 (-21.57,-5.86)**	**0.001**	**-15.18 (-27.65, -2.71)**	**0.02**	0.01 (-0.12, 0.16)	0.81
Adjusted mean (95% CI)		**-15.53 (-24.78, -6.28)**	**0.001**	**-14.06 (-28.76, -0.65)**	**0.04**	-0.05 (-0.22, 0.11)	0.54
Chlorinated solvents							
Not exposed Mean (SE)	616	-25.61 (1.97)		-32.19 (2.97)		-0.62 (0.03)	
Exposed Mean (SE)	151	-36.51 (4.38)		-38.2 (8.11)		-0.67 (0.08)	
Unadjusted mean (95% CI)		**-10.89 (-19.82, -1.96)**	**0.01**	-6.0 (-20.18, 8.17)	0.40	-0.05 (-0.21, 0.11)	0.54
Adjusted mean (95% CI)		**-11.56 (-21.54,-1.57)**	**0.02**	-3.76 (-19.6, 12.07)	0.64	-0.13 (-0.31, 0.04)	0.15
Other solvents							
Not exposed Mean (SE)	471	-24.49 (2.33)		-27.46 (3.26)		-0.62 (0.04)	
Exposed Mean (SE)	296	-32.95 (2.86)		-42.78 (5.29)		-0.64 (0.05)	
Unadjusted mean (95% CI)		**-8.46 (-14.6, -1.17)**	**0.02**	**-13.21 (-26.65, -0.24)**	**0.01**	-0.01 (-0.15, 0.11)	0.81
Adjusted mean (95% CI)		-6.08 (-14.6, 2.43)	0.16	**-13.2 (-26.6, 0.24)**	**0.05**	0.02 (-0.12, 0.18)	0.72
Metals							
Not exposed Mean (SE)	606	-25.6 (1.95)		-29.56 (2.86)		-0.64 (0.03)	
Exposed Mean (SE)	161	-35.87 (4.49)		-47.75 (8.35)		-0.59 (0.07)	
Unadjusted mean (95% CI)		**-10.27 (-18.99, -1.55)**	**0.02**	**-18.20 (-31.99, -4.41)**	**0.01**	0.05 (-0.10, 0.21)	0.52
Adjusted mean (95% CI)		**-11.31 (-21.92, -0.69)**	**0.04**	**-17.54 (-34.32, -0.76)**	**0.04**	-0.07 (-0.26, 0.11)	0.43

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weight, the models with VGDF were additionally adjusted for pesticides and models with solvents and metals were additionally adjusted for both pesticides and VGDF

Table 7.4 Associations between ever exposures to pesticides and decline in lung function

Exposure		ΔFEV₁ (mL/year)		ΔFVC (mL/year)		ΔFEV₁/FVC (%/year)	
	n	β (95%CI)	P-value	β (95%CI)	P-value	β (95%CI)	P-value
All pesticides							
Not exposed Mean (SE)	646	-27.11 (1.94)		-31.93 (3.03)		-0.65 (0.03)	
Exposed Mean (SE)	121	-31.22 (4.95)		-41.1 (8.32)		-0.57 (0.09)	
Unadjusted mean (95% CI)		-4.11 (-13.89,5.65)	0.41	-9.17 (-24.63, 6.28)	0.24	0.07 (-0.10, 0.25)	0.39
Adjusted mean (95% CI)		-2.14 (-12.61,8.32)	0.68	-3.50 (-20.05,13.04)	0.68	0.06 (-0.12, 0.25)	0.47
Herbicides							
Not exposed Mean (SE)	665	-26.97 (1.93)		-31.96 (2.97)		-0.65 (0.03)	
Exposed Mean (SE)	102	-32.85 (5.17)		-42.62 (9.44)		-0.54 (0.09)	
Unadjusted mean (95% CI)		-5.88 (-16.36,4.61)	0.27	-10.66 (-27.25,5.93)	0.21	0.11 (-0.08, 0.30)	0.25
Adjusted mean (95% CI)		-4.86 (-16.0,6.26)	0.39	-6.51 (24.12,11.09)	0.47	0.09 (-0.10, 0.30)	0.33
Insecticides							
Not exposed Mean (SE)	672	-27.22 (1.95)		-32.09 (3.01)		-0.65 (0.03)	
Exposed Mean (SE)	95	-31.57 (4.88)		-42.49 (9.23)		-0.49 (0.09)	
Unadjusted mean (95% CI)		-4.35 (-15.16,6.46)	0.43	-10.4 (-27.51, 6.7)	0.23	0.15 (-0.04, 0.35)	0.12
Adjusted mean (95% CI)		-2.83 (-14.26,8.59)	0.62	-6.5 (-24.57, 11.57)	0.48	0.15 (-0.05, 0.35)	0.14

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weight, the models with pesticides were additionally adjusted for VGDF

7.5.4 Cumulative exposure-unit-years and lung function decline

The associations between cumulative exposure-unit (EU)-years and lung function decline are presented in Table 7.5. Per EU-years increase in cumulative exposure to aromatic solvents, there was a -0.63 mL/year (95%CI; -1.02, -0.24) greater decline in FEV_1 and a -0.96 mL/year (95%CI; -1.56, -0.36) greater decline in FVC. I found significant association between cumulative EU-years to gases/fumes and decline in FEV_1 but no associations were observed with pesticides, herbicides, insecticides exposure and lung function decline.

Table 7.5 Association between cumulative EU-years and declines in lung function

Cumulative Exposures-Unit years	ΔFEV$_1$ (mL/year)		ΔFVC (mL/year)		ΔFEV$_1$/FVC (%/year)	
	β (95%CI) †	**P-value**	**β (95%CI)**	**P-value**	**β (95%CI)**	**P-value**
Biological dust	0.13 (-0.04, 0.3)	0.14	0.14 (-0.12, 0.41)	0.29	-0.0 (-0.003, 0.003)	0.99
Mineral dust	0.09 (-0.05, 0.23)	0.21	0.19 (-0.03, 0.41)	0.09	-0.0 (0.003, 0.002)	0.62
Gases/fumes	**-0.14 (-0.28, -0.0)**	**0.04**	-0.15 (-0.36, 0.06)	0.17	-0.0 (0.002, 0.002)	0.79
VGDF	-0.03 (-0.14, 0.07)	0.54	0.02 (-0.14, 0.19)	0.81	-0.001 (0.002, 0.001)	0.46
Aromatic solvents	**-0.63 (-1.02, -0.24)**	**0.002**	**-0.96 (-1.56, -0.36)**	**0.002**	0.003 (-0.004, 0.01)	0.38
Chlorinated solvents	-0.12 (-0.29,0.05)	0.18	-0.09 (0.36, 0.17)	0.47	-0.001 (0.004, 0.001)	0.42
Other solvents	-0.10 (0.39, 0.19)	0.49	-0.33 (-0.78, 0.12)	0.14	0.001 (0.003, 0.006)	0.65
Metals	-0.04 (0.21, 0.13)	0.65	-0.10 (-0.27, 0.25)	0.93	-0.002 (-0.004, 0.001)	0.22
All pesticides	0.15 (-0.15, 0.46)	0.32	0.6 (0.13, 1.07)	0.01	-0.0 (0.006, 0.005)	0.86
Herbicides	0.33 (-0.11, 0.77)	0.14	0.64 (-0.03, 1.32)	0.06	0.003 (-0.005, 0.1)	0.51
Insecticides	0.09 (-0.24, 0.43)	0.57	0.62 (0.09, 1.13)	0.01	-0.0 (-0.006, 0.005)	0.89

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weight, the models with pesticides were additionally adjusted for VGDF, the models with VGDF were adjusted for pesticides and models with solvents and metals were additionally adjusted for both pesticides and VGDF

7.5.5 Effect modification

I examined if the relationships between occupational exposures and lung function decline were modified by sex, asthma and smoking. Neither asthma nor smoking modified any associations. However, I observed a significant effect modification by sex and cumulative EU-years to aromatic solvents (Table 7.6) for greater decline in FEV_1 ($p = 0.02$) and FEV_1/FVC ratio ($p = 0.01$). Even so, I found that women had fewer cumulative EU-years to aromatic solvents (mean±SD=9.6±15.5) compared to men (mean±SD=16.6±14.6). Figure 7.2 displayed the predicted decline in FEV_1, FVC (Figure 7.3) and FEV_1/FVC (Figure 7.4) ratio that were calculated using the linear estimates from the multiple linear regression models. In this model, women with increasing cumulative EU-years to aromatic solvents had a greater lung function decline. However for men I did not observe any such relationship. I did not observe that sex to modify the associations related to any of the other exposures.

Table 7.6 Effect modification by sex on the relationship between cumulative EU-years to solvents and lung function decline

Cumulative exposure-unit years	Women β (95% CI)	Men β (95% CI)	p-trend for effect modification
Aromatic solvents			
ΔFEV_1 (mL/year)	**-1.44 (-2.26, -0.63)**	-0.37 (-0.81, 0.06)	**0.02**
ΔFVC (mL/year)	**-1.8 (-3.05, -0.55)**	**-0.73 (-1.4, -0.04)**	0.14
ΔFEV_1/FVC (%/year)	**-0.013 (-0.027, -0.001)**	0.008 (0.0, 0.02)	**0.01**
Chlorinated solvents			
ΔFEV_1 (mL/year)	-1.19 (-2.71, 0.33)	-0.11 (-0.28, 0.07)	0.16
ΔFVC (mL/year)	-1.73 (-4.06, 0.61)	-0.08 (-0.35, 0.18)	0.17
ΔFEV_1/FVC (%/year)	-0.013 (-0.039, 0.013)	-0.001 (0.004, 0.002)	0.37
Other solvents			
ΔFEV_1 (mL/year)	0.09 (-0.33, 0.51)	-0.23 (-0.63, 0.16)	0.25
ΔFVC (mL/year)	-0.05 (-0.69, 0.59)	-0.59 (-1.19, 0.007)	0.22
ΔFEV_1/FVC (%/year)	-0.003 (-0.01, 0.004)	0.005 (-0.001, 0.012)	0.09

† Adjusted for sex, height, smoking, pack-years, childhood and adulthood socioeconomic status, childhood and adulthood asthma and sampling weight, the models with solvents were additionally adjusted for pesticides and VGDF

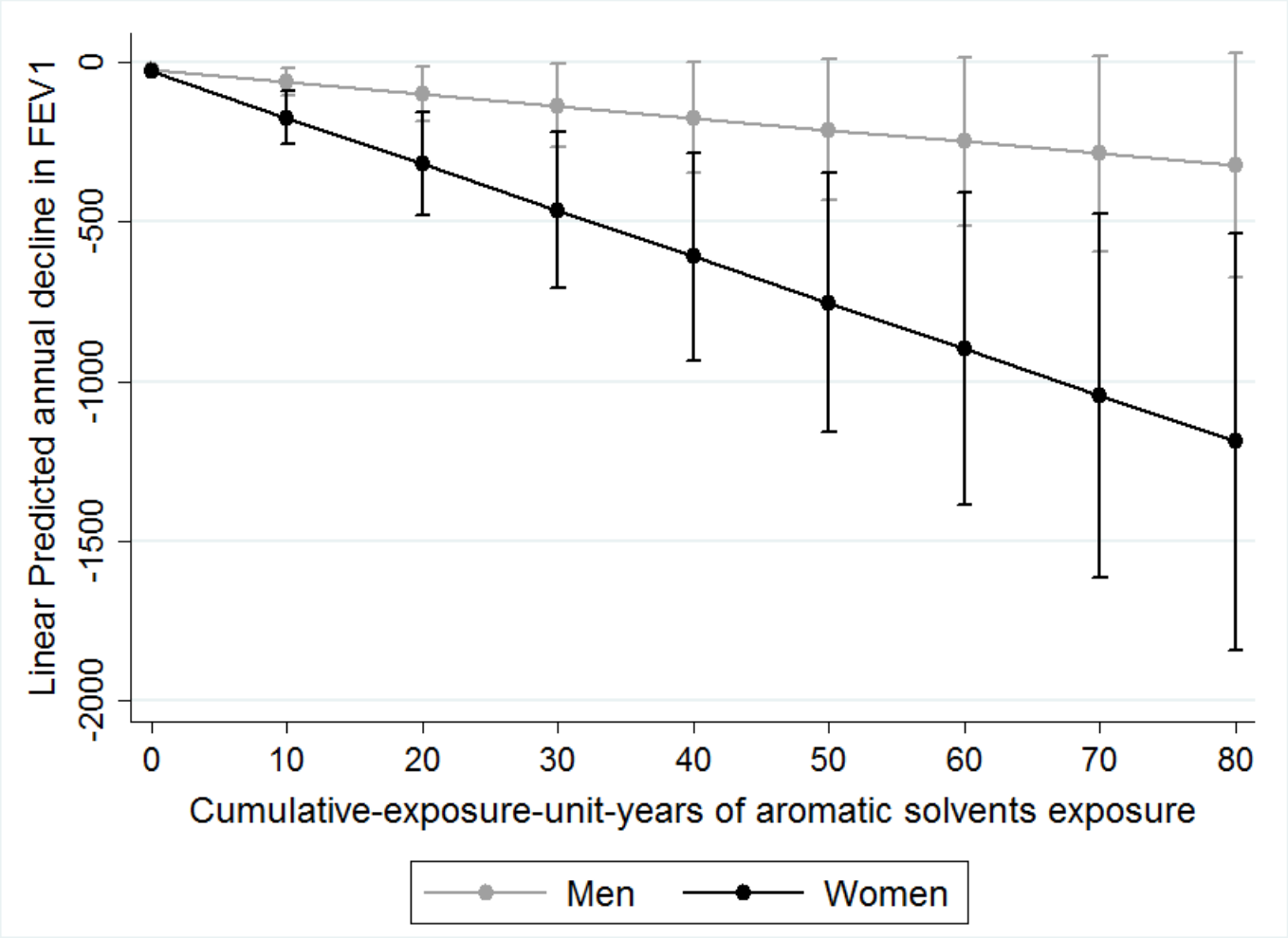


Figure 7.2 The association between cumulative years of exposure to aromatic solvents and linear predicted decline in FEV1, stratified by sex. Circles represent the decline of the FEV1 and the bars represent the 95% confidence interval

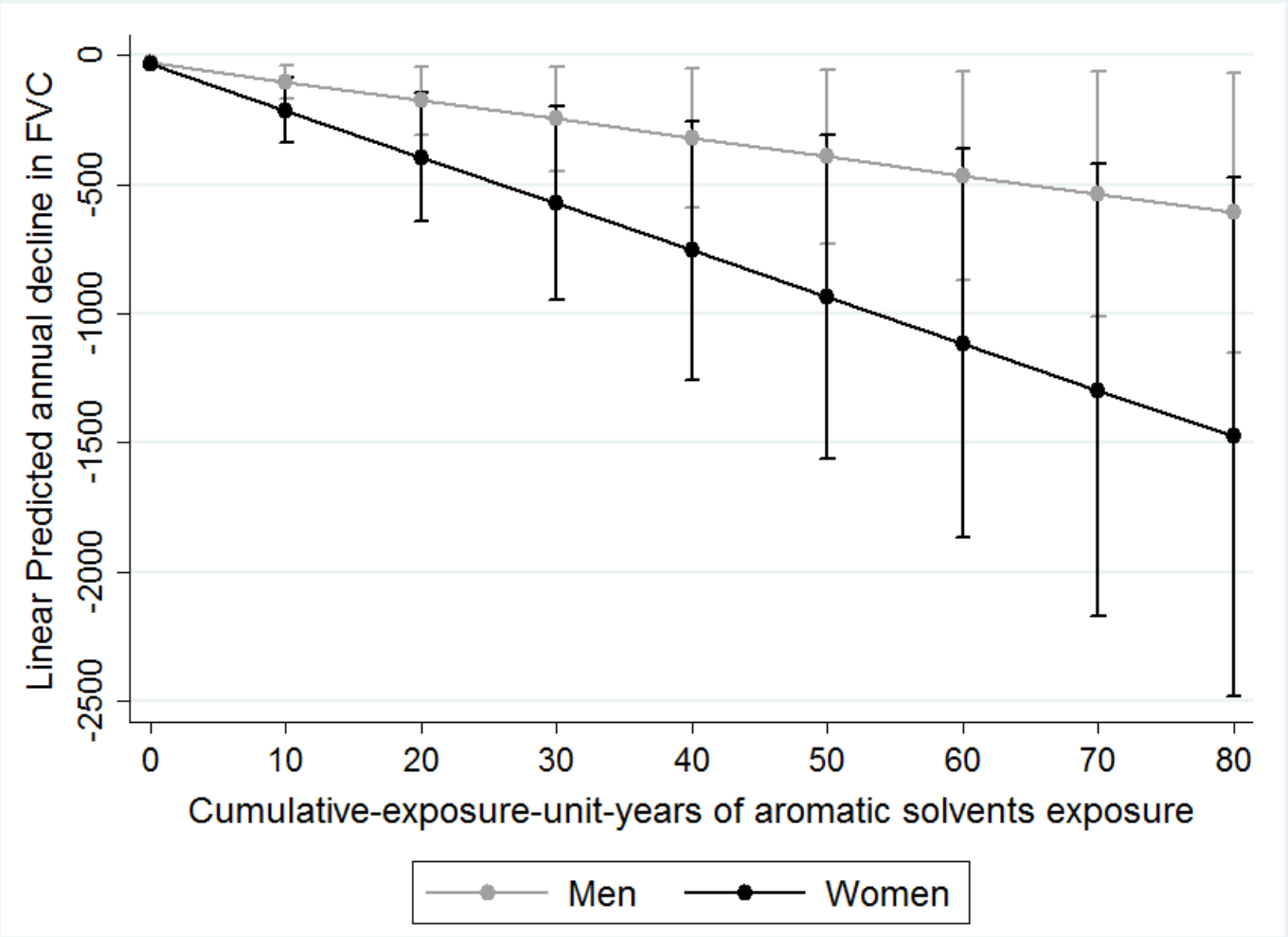


Figure 7.3 The association between cumulative years of exposure to aromatic solvents and linear predicted decline in FVC, stratified by sex. Circles represent the decline of the FVC and the bars represent the 95% confidence interval

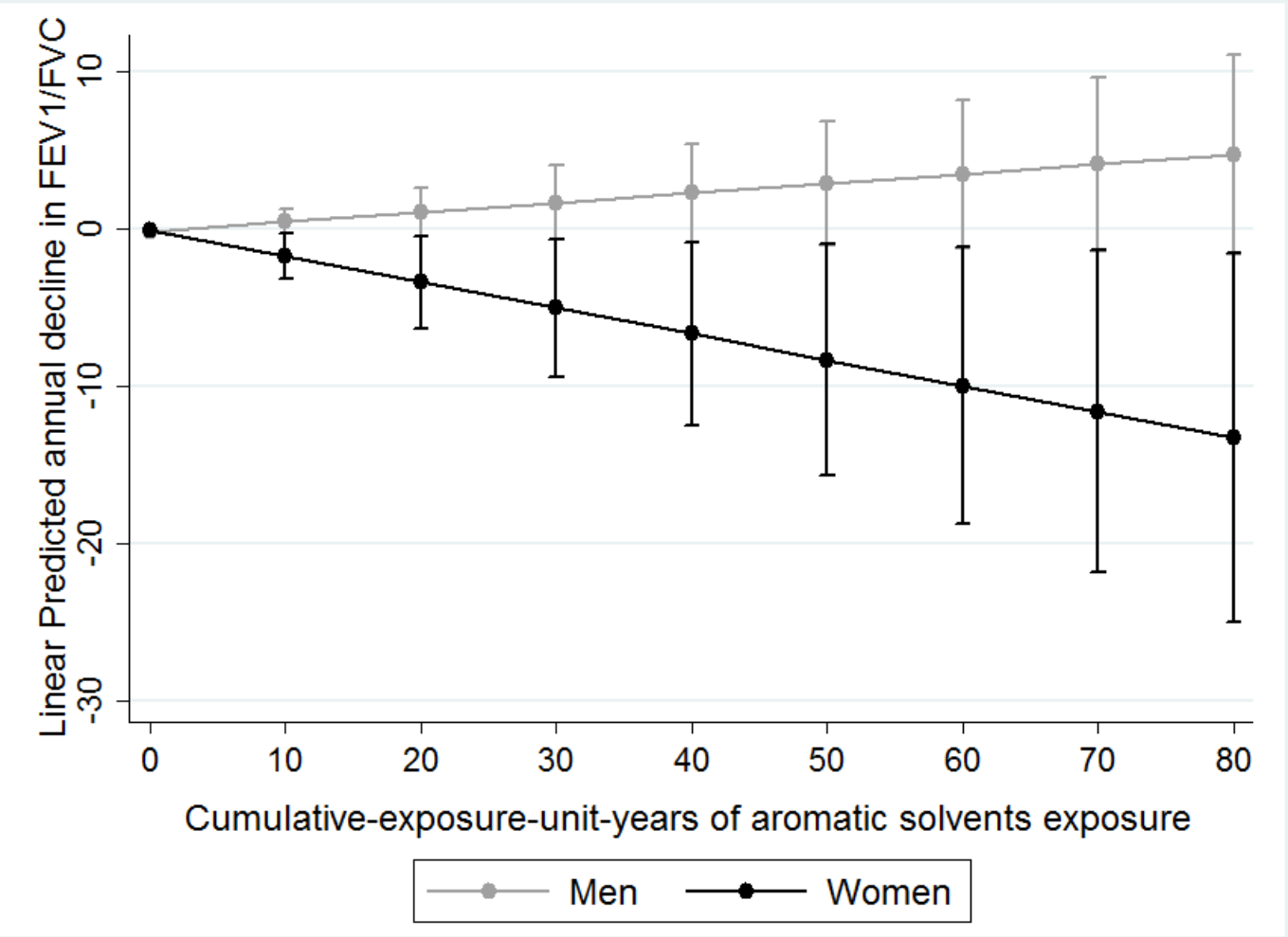


Figure 7.4 The association between cumulative years of exposure to aromatic solvents and linear predicted decline in FEV1/FVC ratio, stratified by sex. Circles represent the decline of the FEV1/FVC ratio and the bars represent the 95% confidence interval

7.6 Chapter discussion

This longitudinal study provides robust evidence that several different classes of occupational exposure were associated with greater lung function decline between the ages of 45 and 50 years. Importantly, I found consistently greater lung function decline, with ever being exposed and cumulative EU-years to aromatic solvents. In particular, I observed significant effect modification by sex of the association between cumulative-EU-years to

aromatic solvents and lung function decline. Women had a greater decline in both FEV_1 and FEV_1/FVC ratio compared to men. I also observed a greater decline in lung function between the ages of 45 and 50 years for those with ever exposed to gases/ fumes, chlorinated solvents, and metals.

Cross-sectional studies have provided some evidence for an association between occupational exposure to solvents and cross-sectional lung function (85, 154), but the findings are contradictory. A cross-sectional study from France found an association between specific solvents (benzene, carbon tetrachloride, degreasing agents, other solvents and epoxy resins) and lower level of lung function (154). Another cross-sectional study from the Netherlands did not find any association between workplace exposure to solvents and lung function (85). Several cross-sectional studies (100, 102, 113, 153) and longitudinal study (24) suggested that solvents exposure was associated with self-reported respiratory symptoms and chronic bronchitis. The longitudinal Zutphen cohort used lifetime work histories to assign workplace exposure to solvents and showed that it is related to chronic non-specific lung disease but no information was reported on lung function decline (24). In this longitudinal analysis I adjusted for co-exposures including pesticides and/or VGDF and also other solvents and chlorinated solvents exposures and found it did not effect the results. My study provides evidence that exposure to solvents is an important risk factor for lung function decline.

Cumulative EU-years to aromatic solvents was associated with greater decline in FEV_1 and FVC, however I did not find the same effects for cumulative EU-years to chlorinated or other solvents. The reason for this differences within the categories of solvents in my study, or could be related with cumulative exposure to those agents, nature and chemical structure of the solvents, the level of exposure and the duration of exposure. For example, some aromatic solvents (e.g. benzene) are absorbed better than chlorinated solvents depending on their composition and porosity, and the absorption is further influenced by temperature and humidity (191). The different job distribution between aromatic and chlorinated solvents in this study may be another explanation for slight variations in the results. For example, a large proportion of my study population (both men and women)

exposed to aromatic solvents but not chlorinated solvents are working in painting, electrical, agriculture, mining, and construction industries, while participants exposed to chlorinated solvents but not to aromatic solvents are working in hand-launderers, pressers, metal, machinery and related trade industries. Slight different exposure to aromatic and chlorinated solvents in different industries that may contain different chemicals resulting slightly different responses (150). Exposure to solvents also depends on the vapor concentration in the workplace and actual cumulative dose and the duration inhaled by the participants. The complex interplay between these factors may also influence lung function decline to different types of solvents (191).

Importantly, despite women reported a lower cumulative EU-years to aromatic solvents compared with men (women median=5.5 EU-years, IQR; 2-12.5, men median=13 EU-years, IQR; 5.5-26), women had a greater decline in FEV_1 and FEV_1/FVC ratio with increasing cumulative EU-years to aromatic solvents. The women in this study exposed to aromatic solvents were field crop and vegetable growers, sculptors/painters/artists, woodworkers, and life science technicians, while men were mostly painters, carpenters, plumbers, pipe-fitters and fire-fighters. The reason women show a greater decline than men remains unknown (27). Possible explanations include differences in the patterns of occupational exposure (27, 28), or due to the presence of female sex hormones (192). Toxins in the airways are metabolized via the cytochrome P450 pathway (27). The female sex hormone estrogen can influence this pathway by causing the up-regulation of the CYP1A1, CYP1A2, CYP2A6, CYP3A4, and CYP1B1 cytochromes. The role of these enzymes in the toxin metabolism pathway leads to increased oxidation of inhaled substance leading to increased oxidative stress in the airways and greater risk of airflow obstruction in females (193). No previous longitudinal studies investigated the effect of lung function on men and women when exposed to solvents. Few cross-sectional studies conducted on different occupational exposures and reported significant association with airflow obstruction as measured by lung function in women but not men (19, 173). The only study that examined longitudinal lung function decline in the general population did not find any difference between men and women when exposed to biological dust, mineral dust and gases or fumes (84). In my study, I also did not find any difference between men and women with ever

exposure to solvents, but I found association for women with increasing cumulative EU-years. My findings also suggest that exposure to solvents largely depends on the cumulative exposure rather than ever exposure.

My analysis shows association between ever exposure to gases/fumes and a greater decline in FEV_1. The European Community Respiratory Health Survey (ECRHS) (84) and the Vlagtwedde-Vlaardingen cohort (90) studies used the ALOHA JEM to assess occupational exposure, but they did not find an association between ever exposure (low or high) to gases/fumes with lung function decline. The Vlagtwedde-Vlaardingen cohort study found a borderline significant association with cumulative exposure to VGDF (90) but their association with cumulative exposure to VGDF disappeared after adjustment for possible co-exposure to pesticides. The Vlagtwedde-Vlaardingen study used the current job to assign exposure, and there is a possibility that this study underestimated the true impact of gases/fumes exposure on lung function decline. I used lifetime work history calendars up to the age 45 years, and my observed association with workplace exposure to gases/fumes remains even after adjustment for co-exposure to pesticides.

I found an association between ever exposure to metals with greater decline in FEV_1 and FVC, and this is consistent with previous workplace based longitudinal study that found an association with cobalt dust exposure and lung function decline (157). Subjects exposed to metals in my study described themselves as working in metal or steel industries such as motor vehicle mechanics and fitters, sheet metal workers, welders and flame cutters and agriculture or industrial machinery mechanics. A recent meta-analysis included longitudinal studies on welders also found an association between exposure to welding fumes and lung function decline (158). This raises the possibilities that the observed association with ever exposure to metals could be related to inhalation exposure that is, any amount of metal inhalation may cause pulmonary surfactant impairment resulting in greater lung function decline.

My study had several strengths including an extensive dataset that allowed for adjustment for a wide range of confounders including childhood and adult asthma and

socioeconomic status at both follow-up and co-exposures as indicated. Using lifetime work history calendars and not just the current or most recent job facilitated the calculation of cumulative-EU-years, which is critical to understanding the nature of exposure-outcome relationship, particularly for chronic disease. My exposure was classified based on a JEM that is less likely to be affected by recall bias but might result in non-differential misclassification bias due to potential heterogeneity of exposure within a given job title. However, this misclassification typically results in a bias towards the null resulting in an underestimation of the true effect. Multiple comparisons were performed but the associations were consistent across several lung function parameters, suggesting these findings are less likely to be related chance. Furthermore, occupational history data were collected at 2002 to 2008 follow-up, and there is a chance that participants with respiratory or lung function problems could have changed their occupations during the follow-up time from high exposed to low exposed job or vice versa or changed their work environment to reduce the level of exposure. This may result in underestimation of the observed associations between occupational exposure and lung function. I used pre-BD lung function measurement, which is one of the important limitation in my study. However, the correlated exposure between three categories of solvents likely to affect the association observed in this study, however, my stricter control of confounders and co-exposures may be helped to rule out this possibility.

In conclusion, my study provides evidence that ever exposure and cumulative-EU-years to aromatic solvents is associated with greater decline in lung function in this general Australian population. I also provide a novel insight of effect modification by sex on the relationship between cumulative EU-years to aromatic solvents and greater lung function decline. The effect of aromatic solvents is not due to greater exposure in women but due to greater susceptibility. This greater lung function decline in women may subsequently increase the risk of obstructive airway disease in their later life and therefore contribute to the burden of morbidity and mortality associated with airway disease.

Chapter 8 Overall discussion

8.1 Thesis summary

COPD is an important cause of worldwide morbidity and mortality. For decades, COPD has been characterised by fixed AO as measured by post-BD spirometry and defined by reduction in the ratio of $FEV_1/FVC<0.7$ and $FEV_1/FVC<LLN$. Chronic bronchitis, and respiratory symptoms are also considered as a predictor of COPD or associated with abnormal lung function. Despite tobacco smoking being the major risk factor for COPD, it is also suggested that occupational exposure to dusts, gases, and fumes are a risk factor for developing COPD. However, population-based studies examining these associations are limited and have had some significant limitations, including 1) use of pre-BD spirometry to define COPD, 2) failure to investigate certain common occupational exposures; 3) the use of various occupational exposure assessment tools causing significant heterogeneity between studies; and 4) limited investigation of lifetime and cumulative occupational exposures, which are important for investigating chronic diseases. These limitations led me to conduct the following investigations in my thesis 1) perform a systematic review and meta-analysis of the existing studies exploring the association between occupational exposures assessed by a JEM and COPD (Chapter 3), 2) investigate the association between common exposures with known impact of repiratory outcomes and COPD, specifically pesticides and herbicides (Chapter 5) and solvents and metals (Chapter 6); and 3) explore the association between occupational exposures and lung function decline (Chapter 7).

8.2 Chapter 3- summary

My systematic review and meta-analysis examined the association between occupational exposure and COPD in population-based studies. It was the first study to assess this relationship using robust measures of both exposure and outcome. I only included studies that used the ALOHA JEM, which is specifically designed for COPD, and spirometry, which is the gold standard to define COPD. My analysis revealed that occupational exposure was significantly associated with an increased risk of COPD and chronic bronchitis. I found an overall significant association between low exposure to mineral dust and high exposure to gases/fumes and COPD. I also investigated the association between these exposures and chronic bronchitis, finding that low and high exposure to biological dust and mineral dust

was associated with chronic bronchitis. Most studies used one of two common definitions to define COPD, either the GOLD fixed cut-off definition ($FEV_1/FVC<0.7$) or the lower limit of normal definition ($FEV_1/FVC<LLN$). The effect estimates I found in my meta-analysis differed according to which definition was used, with only significant associations being observed with the $FEV_1/FVC<0.7$ definition, not the $FEV_1/FVC<LLN$ definition.

The use of JEMs in population-based studies is ideal to assign exposures, as JEMs are less affected by recall bias and differential misclassification of exposures because they assigned exposures based on reported job title and do not rely on self-reported exposure assessment (16). The outcome of COPD in all included studies in my review, with the exception of one study (103), was defined by pre-BD spirometry, which I identified is a major limitation of current literature exploring this relationship. The post-BD spirometry is recommended by the International Guidelines to define COPD to overcome confounding related biases (1, 12, 13). Overall, my systematic review and meta-analysis confirmed the association between occupational exposure and COPD however it also highlighted several limitations in the existing literature. These limitations include: 1) use of pre-BD spirometry; 2) inconsistent use of COPD definitions (either $FEV_1/FVC < 0.7$ or $FEV_1/FVC <LLN$ or both); 3) very few studies investigated this association; 4) the study age group containing a large number of participants less than 40 years of age and therefore less likely to have developed the chronic outcome; 5) failure to use lifetime work histories to assess all possible occupational exposures; and 6) inadequate management of possible confounding. My review confirmed the need for more population-based studies to address these issues.

8.3 Chapter 5- summary

My first original data analysis investigated the association between occupational exposure and COPD as defined by fixed AO, chronic bronchitis, and respiratory symptoms. My study used two measures of occupational exposure; ever exposure and cumulative EU-years. Overall, I found a consistent significant association between ever exposure and cumulative EU-years to all pesticides and herbicides and fixed AO. I also found significant association between ever exposure to pesticides and herbicides with chronic bronchitis, and

respiratory symptoms. In addition, ever exposure to biological dust, mineral dust, gases/fumes, and VGDF were only associated with fixed AO in non-asthmatics.

A previous study examining the association between pesticides and AO was limited by the used of pre-BD spirometry and using most recent or current job to assign occupational exposure (85). My work has addressed these limitations by using post-BD spirometry and lifetime work history calendars. My study added to the body of evidence describing an association between pesticide exposure and COPD. I also observed effect modification by asthma status on the association between fixed AO and biological dust, mineral dust and gases/fumes, and VGDF exposure. Those without asthma have an increased risk of fixed AO if exposed to biological dust, mineral dust, gases/fumes, and VGDF. Those with asthma did not have an increased risk of fixed AO if exposed to any of these exposures. Overall, my analyses have provided further evidence to suggest an association between pesticides and fixed AO, chronic bronchitis, and respiratory symptoms.

8.4 Chapter 6- summary

My second original analysis investigated the association between COPD as defined by fixed AO and occupational exposure to solvents and metals. I also explored fixed AO with low $D_L$co, which is an indicator for emphysema like COPD phenotype. Very few studies have investigated the association between solvents (aromatic, chlorinated and other solvents) and metal exposure in relation to fixed AO. In this analysis, I found a significant association between fixed AO and ever exposure to metals. In the main analysis, I did not find any association between fixed AO and ever exposure and cumulative EU-years to any types of solvents. However, I identified effect modification by sex in the relationship between fixed AO and cumulative EU-years to chlorinated solvents. For middle-aged women, I found that increasing cumulative EU-years to chlorinated solvents was significantly associated with fixed AO and fixed AO plus low $D_L$co.

There is limited and inconsistent evidence from population-based studies that assessed the association between exposure to solvents and fixed AO. Those that have been conducted, have some major limitations which were addressed in my current analysis. This

analysis further advanced our understanding on the relationship between occupatonal exposure to solvents and fixed AO. This is the first study to show that increasing cumulative EU-years to chlorinated solvents increased the risk of fixed AO and fixed AO with low D_Lco in women but not men although the mean cumulative exposure is less in women. My analysis emphasizes the need to utilize post-BD spirometry to define COPD which allows adequate consideration of all possible covariates, especially for the middle-age population.

8.5 Chapter 7- summary

In my thesis, I also investigated the association between occupational exposures and lung function decline using the longitudinal follow-up data within the TAHS cohort. In this study, I found that both ever and cumulative EU-years to aromatic solvents were associated with a greater decline in lung function between 45 and 50 years of age. Ever exposure to gases/fumes, chlorinated solvents, and metals were also associated with greater decline in FEV_1. Along with this main effect, I also found effect modification by sex in the relationship between cumulative EU-years to aromatic solvents and lung function decline. Women in my study had a greater decline in FEV_1 and FEV_1/FVC ratio with increasing cumulative EU-years to aromatic solvents.

Only a few longitudinal population-based studies have investigated the association between occupational exposure and lung function decline and those that have, have some significant limitations. My work has addressed these limitations by adjusting for a wide range of confounders including asthma at both follow-ups and co-exposures. Furthermore, none of the previous studies have assessed separately aromatic solvents, chlorinated solvents, other solvents, and metals. My study is the first to investigate this relationship in a population-based sample, and I found a consistent association with lung function decline. This study importantly clarified that middle-aged women exposed to aromatic solvents in this study have a greater decline in their lung function despite having had fewer cumulative EU-years to aromatic solvents compared to men. This finding also raises the possibility of greater susceptibility in women exposed to aromatic solvents.

I found the effect of asthma status on the relationship between occupational exposure and fixed AO varied depending on the occupational exposure. For example, I found an

increased risk of fixed AO in those without current asthma when exposed to biological dust, mineral dust or gases/fumes but no effect in those with current asthma. I did not observed the same effect for pesticides or herbicides (Chapter 5), nor for solvents or metals exposure (Chapter 6). This difference indicates that the association present with the exposure to pesticides or herbicides, solvents, and metals were independent of current asthma. Whereas the presence of effect modification by current asthma with dust group of exposure suggest the presence of healthy worker effect, that is, asthmatics who remain in the study are relatively unaffected by these occupational exposures. It also may suggest that asthma alone is a significant risk factor for fixed AO in middle-age and additional occupational exposure does not substantially increase the risk observed at this age.

I also found a slightly different association with chlorinated and aromatic solvents in Chapter 6 and Chapter 7. The different job distribution between aromatic and chlorinated solvents in our study may be the explanation for slight variation in the results. For example, a large proportion of our population (both men and women) exposed to aromatic but not chlorinated solvents were working in painting, electrical, mining, and construction industries. While participants exposed to chlorinated but not aromatic solvents were working as hand-launderers, pressers, metal, machinery and related trade industries. Slightly different exposures to aromatic and chlorinated solvents in different industries that may contain different chemicals may result in different responses (150). Exposures to solvents also depends on the vapor concentration in the workplace and actual cumulative duration worked by the participants. The complex interplay between these factors may also influence lung function decline to different types of solvents (191).

My findings also suggest that sex modified the association between exposure to solvents and fixed AO and lung function decline but not for other occupational exposures. Interestingly, I found the women in my study had a lower prevalence and fewer years of exposure to solvents than men, but had a greater risk of fixed AO than men. This multiplicative interaction effect raises the possibility of a greater degree of susceptibility in women as a result of inhaled solvents than men. The null effect with other occupational exposures may be related to the job distribution and task difference between men and women resulting in no effect modification, or the chemical structure of solvents that may increase the risk in women but not in other exposures.

I have discussed these findings in more detail in each of the results chapters and summarized them in this chapter. In this overall discussion chapter, I have expanded on the common issues associated with occupational exposure assessment, analytic issues, and discuss the strengths and limitations of my doctoral work. The potential for the findings to advance the knowledge in the field is also discussed.

8.6 Study strengths and limitations

8.6.1 Study design

The main strength of my doctoral work is that I used data from the TAHS, one of the world's longest-running general population-based cohort studies of respiratory health. The main strength of the TAHS is the collection of lifetime work history calendar (WHC) and longitudinal follow-up starting from early life into middle age. The TAHS has prospectively collected questionnaire data from childhood into middle age on a wide range of risk factors and possible confounders. Importantly, TAHS also has repeated measures of lung function starting in childhood with the availability of post-BD spirometry at age 45 years. TAHS has excellent tracing and postal survey response rates over time (29). Although not technically a birth cohort since all participants were born in 1961, the participants were recruited into the study at age 7 years and they are all within a narrow age range at each follow-up thereby minimizing any age-related bias. Furthermore, all participants were recruited from the island state of Australia called Tasmania and has a homogenous ethnic structure with over 95% of the TAHS participants being of caucasian ethnicity reducing any possible ethnic related biases.

As with all longitudinal studies, TAHS has had attrition over time but overall the response rates to the surveys have been very high (29). The main focus of my work was the 2002-2008 follow-up study which attempted to survey all cohort members from the first time since 1968 (baseline study). In this follow-up, an excellent response rate to the postal survey was achieved due to the detailed and careful follow-up (29, 177). Details of which have been described in the method section of this thesis (Chapter 4). Overall, in the 2002 to 2008 follow-up, the response rate was 78% in the postal survey and 58% in the laboratory study. The percentage of non-responders was 27% as participants withdrew from the laboratory study

but did participate in the postal survey. In order to address any issues of possible non-response bias in my analysis for Chapter 5 and Chapter 6, I compared the baseline characteristics between responders and non-responders and included any factors that were significantly different between the two groups in my statistical analysis. Additionally, I used inverse-probability sampling weights as an additional variable in my models and observed if the inclusion of these weights altered the estimates by more than 10%. Overall adjusting for these weights did not alter estimates as presented in the analysis therefore the enrichment is unlikely to have had an impact on my results.

8.6.2 Occupational exposure assessment

The strength and credibility of evidence from occupational studies depends on the validity and precision with which the work history is reported and then the occupational exposures assessed or assigned. In TAHS a lifetime WHC has been collected using a standardized questionnaire recording the job description, job title, name of employer and duration of employment. The work history calendar in TAHS was designed with the collaboration of occupational epidemiologists and industrial hygienists. The collection of complete lifetime work history is less prone to recall bias because all jobs are recorded irrespective of any known or perceived hazardous exposure (16, 194). Collection of lifetime work history also allows for examination of cumulative exposure which is important for chronic disease and diseases with long lag periods from exposure to disease onset (194). In this thesis, I used two measures of occupational exposure, ever exposure and lifetime cumulative exposure. Ever exposure is likely to be accurate if collected from a reliable source but may be subject to misclassification which if non-differential or random may result in a reduced relative risk or an association being missed altogether. Cumulative exposure unit years or any measure of duration of exposure is a surrogate for dose and can be used to explore the possibility of a dose-response relationship.

Despite their strengths, the use of lifetime work history calendars as the occupational data collection method does have some limitations (88). Incomplete, missing or poorly completed work history calendars are an issue. In my WHC, I had some missing and incomplete information including missing job title, industry description or duration of

employment. I had participants who had part of their information missing in their WHC (e.g, they had 10 jobs listed with five jobs missing information). I excluded participants who did not report year started and ended in particular jobs from cumulative exposure analysis but did include them in the ever exposure analysis. Details of the handling of the missing information in the work history calendar is described in Chapter 4 section 4.4.1 in this thesis.

The use of WHC to collect lifetime work histories in a uniform and consistent manner relatively free of recall bias is the first step in assigning occupational exposure (88). The second step is assigning exposure to a particular agent which in population-based studies is most accurately done via a JEM to minimize exposure misclassification. JEMs provide a rapid way to transform coded occupational titles into potential exposures (65). I completed all job-coding to ensure consistency and my supervisor Dr Benke, an experienced occupational hygienist checked the coding.

The limitations associated with JEMs include the potential for misclassification of exposure by the inability of JEMs to take into account variability of actual exposure within each job title (16). This is particularly an issue when the job title is composed of many tasks with high variability in exposure between the different tasks (195). Avoiding this type of misclassification is difficult but can be achieved via expert assessment of specific job descriptions within a job category and the reassignment of exposure if required. We did not do this in our study as we did not have detailed job descriptions. However, studies that have performed this labour-intensive expert judgement step have found that substantial changes were only made in a few categories and they had very little impact on the specific disease risks associated with these exposures (196).

8.6.3 Definitions of COPD and lung function

The main outcome in my thesis, COPD was defined based on spirometric criteria. I used post-BD lung function measurements to define fixed AO, which is recommended by the ATS/ERS guideline (1). In my thesis, I used both GOLD (55) and LLN definition (48), to define fixed AO. Both these criteria recommend using post-BD spirometry, which is one of the major methodological strengths in my PhD.

The TAHS lung function measurements also additionally measured gas transfer factor such as $D_L$co. In my thesis, low $D_L$co was analyzed in combination with post-BD fixed AO. Reduced gas transfer factor ($D_L$co) in combination with fixed AO suggests the presence of an emphysematous-COPD phenotype (197). Low $D_L$co in combination with fixed AO is not a widely accepted definition to identify emphysema, which is frequently defined by high-resolution computed tomography (CT) (198). However, CT scans are not feasible for large scale epidemiological studies and so despite some limitations to using $D_L$co in combination with fixed AO to define emphysema, it has been used to define emphysematous related changes in past large epidemiological studies (19, 199).

Along with the objective measurement of spirometry to define fixed AO, I also used questionnaire-based self-reported chronic bronchitis and respiratory symptoms such as cough, phlegm, and dyspnoea. All these definitions were solely based on participant's response, so, there is a chance that it may introduce some degree of information bias into the analysis. However, it is also very common in epidemiological studies to rely on the questionnaire-based responses due to accessibility and feasibility. The questions used in the TAHS questionnaire were validated questions from several other long-running international cohorts such as ECRHS (200) and BOLD (26) studies and have been widely used in respiratory studies (19, 127, 131).

The analysis presented in Chapter 7 on lung function decline used data from the age 45 and 50-year follow-up studies. The main focus of the age 50 follow-up was a methacholine challenge test and so only pre-BD spirometry was performed at this follow-up. Hence my analysis of lung function decline presented in chapter 7 is based on pre-BD decline between age 45 and 50 years. However evidence from the ECRHS suggests that in middle-aged adults, pre-BD AO can correctly identified the large majority of subjects with fixed AO 9 years later (201). This highlights the importance of repeated measurements over time and its ability to be highly predictive of future fixed AO risk.

8.6.4 Confounding variables

The TAHS dataset includes a wide range of variables that may be associated with exposure and outcome variables and could be treated as potential confounders and effect modifiers in the regression models. The prospectively collected data in TAHS from early childhood to adulthood enabled me to take into account childhood asthma and childhood socioeconomic status both at the age of 7 and 12 years. In contrast, no previous studies have been able to adjust for all the identified confounding variables because of a relatively low number of participants in the follow-up or lack of early life exposure data (19, 20, 83-85).

When investigating the association between occupational exposure and fixed AO the potential confounding effect of asthma is an important factor to take into consideration. Most of the international guidelines report that differentiating asthma from developing AO is almost impossible in epidemiological studies (55). A history of adult asthma can lead to the development of fixed AO (202), and asthma in early life can lead to the development of COPD in later life (203). However, the presence of asthma either in early life or in adult life may also lead to alterations in occupational exposure (204). Therefore, in my analysis I included both childhood and adulthood asthma as a confounder in the regression models.

Adjustment of socioeconomic status (SES) in occupational studies is a matter of debate. SES could be strongly associated with occupation and COPD is associated with low SES (205). SES is a complex index that is also comprised of other elements such as education, occupation, social class, smoking, housing conditions, diet, and ethnicity (206). Adjustment for SES is sometimes performed to take into account some hidden occupational confounding factors such as job-related stress or psychological factors(206). However, the possibility of over adjustment with SES still exists, but it may lead to underestimating the association (206). I used the Socio-Economic Indexes for Areas (SEIFA indexes) from the Australian census data to adjust for childhood and adult socioeconomic status (186). I used the Index of Education and Occupation (IEO) variables that focused on the skills of the people required in different occupations. A high level of IEO score indicated that people who lived in that area had high qualifications and were involved in highly skilled jobs.

8.7 Association or causation

The aim of my doctoral work was to investigate the association between occupational exposure and COPD as defined by fixed AO in middle-aged adults. The ultimate goal of my research was to identify agents that are causally associated with the development of disease. Although epidemiological studies cannot directly prove causation they can provide evidence that collectively suggests the strong likelihood that causality exists. Bradford Hill (207) proposed a set of criteria that if met could demonstrate that causation exists between an exposure and the disease outcome. These criteria are (1) A sufficient strength of association; (2) A temporal relationship between exposure and outcome; (3) A dose-response relationship; (4) Consistency or reproducibility; (5) Biological plausibility; (6) Coherence; (7) Specificity of the effect; and (8) Analogy. Table 8.1 explores how the main results of my thesis (Chapter 5 and Chapter 6) meets these criteria.

Table 8.1 The results of my thesis by the Bradford Hill criteria to illustrate a possible causal effect relationship

Criteria	Pesticides exposure and fixed AO	Solvents exposure and fixed AO
Strength of association	The association between ever exposure to pesticides and herbicides and fixed AO was strong in the range of RR=1.7 to RR=2.0	There was a weak to moderate association between cumulative EU-years to chlorinated solvents and fixed AO in women (RR=1.34).
Temporal relationship	My study was cross-sectional with both the exposure and outcome recorded at the same time so I am unable to determine when fixed AO started relative to occupational exposure.	I assessed lifetime occupational exposure to age 45 years and its impact on lung function decline between 45-50 years of age.
Dose-response relationship	I observed increasing cumulative EU-years to pesticides and herbicides was associated with fixed AO.	I observed increasing cumulative EU-years to chlorinated solvents was associated with fixed AO in women but not in men.
Consistency or reproducibility	Pesticide exposure has been associated with fixed AO in another population based study in other country (85).	I was the first to investigate the effect of chlorinated solvents with fixed AO and aromatic solvents with lung function decline in population-based study. However, previous studies have found associations between overall solvent exposure and respiratory symptoms (23, 24, 102).
Biological plausibility and coherence between epidemiological and experimental evidence	The association of pesticides with respiratory diseases is biologically plausible and consistent with previous knowledge. This includes many studies that have observed respiratory symptoms such as cough, phlegm, asthma and chronic bronchitis in farmers and other workers with known high pesticide exposure.	The association I have observed between exposure to solvents and fixed AO and lung function decline is biologically plausible. It is also consistent with previous findings that have observed the association with respiratory symptoms of chronic non-specific lung disease.
Specificity of the effect	Pesticide exposure is known to cause a variety of systemic effects. A primary route of exposure is via inhalation and respiratory effects are a known consequence of exposure.	Solvents exposure may also cause respiratory effects. On inhalation, the solvents may also cause chronic airway disease as a consequence of chronic exposure.
Analogy	The effect of pesticides on fixed AO is very similar to other pesticide induced respiratory symptoms such as chronic bronchitis. Furthermore, fixed AO can be caused by other inhaled irritants such as dust, gases and fumes.	The solvents and fixed AO is similar to other solvents induced respiratory symptoms such as chronic non-specific lung disease (CNSLD).

Overall, concerning the causality within this population-based study after adjusting for a wide range of confounding factors from childhood to adulthood, I found consistent significant association which supports most of the Bradford Hill's criteria to conclude that there is a causal relationship between occupational exposure to pesticides, and solvents and fixed AO. Furthermore, the results with effect modification by sex in the relationship between occupational exposure to solvents and fixed AO and lung function decline may indicate that certain occupational exposures are influencing the risk and acting as a modifiable risk factor in this middle-aged adult cohort.

Chapter 9 Recommendations and conclusions

In this chapter, I present recommendations based on my findings that can be implemented to public health and future research activities, followed by overall concluding remarks.

9.1 Recommendations

Although occupational exposure is often not recognized as a causative agent in clinical practice, findings from this thesis highlighted that a substantial burden of fixed AO is associated with certain occupational exposures. The reason for lack of recognition of occupational exposures in the aetiology of fixed AO by clinicians could be related to the difficulty in diagnosing occupation related fixed AO at an individual level. Based on the findings of this thesis, I have a few recommendations for clinicians to better identify workplace exposure in symptomatic patients.

9.1.1 Clinical recommendations

In Australia, the current screening guidelines by the Lung Foundation Australia (LFA) recommend the use of a screening symptom checklist that includes occupational exposure as an important potential risk factor (208). The recommendation is that individuals over 35 years of age without pre-existing COPD be screened using this checklist along with a COPD screening device. Individuals with an FEV_1/FEV_6 cut-off < 0.75 and with at least one of the items on the screening checklist should be recommended for diagnostic spirometry testing by their health care provider. The LFA checklist recommends that individuals aged 35 years or older who may be at risk of COPD and meet at least one of the following criteria should undergo screening:

- Smoker or ex-smoker,
- Works or worked in a job where he / she is/was exposed to dust, gas, or fumes,
- Cough several times most days,
- Cough up phlegm or mucus most days,
- Out of breath more easily than others of a similar age,
- Experience chest tightness or wheeze,
- Have frequent chest infections.

International GOLD guidelines (2) and the ATS/ERS Task force (1, 41) also recommend considering COPD in any patient with above-mentioned respiratory symptoms along with a history of exposure to risk factors, such as smoking and/or occupational exposures to dust, gases or fumes. The results of my thesis provide further evidence to help refine the screening symptom checklist. My findings of an increased risk of fixed AO in those exposed to pesticides, herbicides and solvents suggest including these occupational exposures in the checklist. It is important not only ascertain the information on the current occupation, but also a full occupational history. Furthermore, periodic health surveillance by occupational and other physicians needs to be conducted among exposed blue-collar workers, regardless of sex.

My work has shown some important effect modification by sex and history of asthma indicating that occupational exposure risk may vary in certain sub-groups in the general population. These results also suggest that those with pre-existing asthma may not have additional risks associated with certain occupational exposures in middle-age population. This may be due to later job changes to reduce the level of exposure or may indicate a healthy worker hire effect. Therefore, in clinical practice, it is important to collect occupational histories for patients with a history of asthma, chronic bronchitis or existing COPD, and patients with reduced lung function in spirometry.

9.1.2 Public health recommendations

9.1.2.1 Pesticide exposure control in the workplace

Findings from this work present strong public health messages for the population at large, at-risk subgroups and implications on workplace policy and practices. On the basis of these findings, a significant proportion of the Australian working population is still exposed to pesticides and their subgroups despite strict pesticide, herbicide and insecticide control guidelines in Australia (209). Australian state and territory guidelines for the safe use of pesticides in workplaces recommend a risk management protocol to minimize occupational exposure to pesticides (210). This includes, but is not limited to:

- Identification of pesticide hazards in the workplace;
- Assessment of risk by pesticides, in storage and transport;

- Determining and implementing proper measures to control the risk and improving existing control measures;
- Appropriate supervision to control pesticide exposure;
- Recording work procedures set up for the workplace;
- Checking the success of control measures.

The control of pesticides should include pesticide processing and handling activities such as manufacturing, production, import, transport, sale, supply, storage, application and proper disposal of pesticides and their containers to ensure safety and to minimize the adverse health effects associated with pesticides (211). For hazardous substances, such as pesticides and herbicides, manufacturers, suppliers, and importers need to consider implementing the following steps:

- Ensuring proper training and health information on pesticide exposure and safe handling of pesticide should be established and strengthened.
- Legislation to control and regulate overall pesticide use by reducing the availability of pesticides.
- Requirements to use comfortable personal protective equipment when handling and applying pesticides.
- Ensuring proper labeling of pesticide containers using appropriate symbols and pictograms, hazard signs, written instructions and warnings whenever possible.
- Undertaking, recording, reviewing and revising risk assessments in the workplace (209).

Occupational health monitoring may be recommended in order to confirm pesticide exposure control in the workplace. This includes atmospheric control, health surveillance or both.

Personal protective equipment (PPE) is the last line of defence against occupational exposure to pesticides. For controlling fixed AO and other respiratory diseases associated with workplace exposure to pesticides, respiratory protective devices or respirators need to be used correctly by the workers to ensure that the workers breathe air without contamination

(209). For protection against organic vapors, the respirator needs to be fitted with an appropriate gas filter. This will help to protect against the types of pesticides that generate mists, dust particles or solvents that produce organic vapors (209, 210).

9.1.2.2 Solvent exposure control

My thesis identified exposure to solvents as a risk factor for fixed AO and decline in lung function. I found women to have a greater risk than men, even with fewer years of exposure to solvents. Jobs with exposure to chlorinated solvents included dry cleaners, laundry pressers, sculptors, painters, decorators and commercial designers, chemists, hairdresser, and beauticians. On the other hand, jobs with aromatic solvent exposure included painters, electricians, agriculture workers, miners and construction workers. Therefore, women handling chemicals and solvents in some of these typically small businesses need to be trained in safe handling of hazardous chemicals and substances. Australian state and territory guidelines for the safety of small businesses recommends a health and safety assessment checklist to identify risks and control hazards at the workplace (212). Furthermore, exposure control can be done by applying the basic principles of the "hierarchy of control" for small industries (213). Hierarchy of control for small businesses is considered the most effective and appropriate method to control hazardous occupational exposure. These strategies include:

1) Elimination: Complete or partial removal of chemical/solvent exposures from the workplace by using an alternative material or by using a physical method or by using a non-hazardous substance instead of chemicals/solvents.

2) Substitution: Replace harmful chemical agent from the workplace or minimize exposure. For example, use a water-based spray instead of an organic solvents-based spray.

3) Isolation: Separate people from the exposure by using a distance or barrier.

4) Engineering controls by using the total or partial enclosure with exhaust ventilation or using downdraft ventilation for nail product application.

5) Administrative controls such as transfer or change job sites or rotation of employees or change roster schedule, limit frequency of exposure and/or providing suitable washing facilities.

6) Personal protective equipment: It is also important to avoid handling harmful chemicals or solvents by wearing personal protective clothing at the workplace, even for a short duration of exposure. Protective clothing and equipment are recommended for employers, employees, supervisors and visitors. These include masks, aprons, gloves, head protection, safety glasses and respirators to avoid harmful exposure to solvents. It is also important that employees have adequate knowledge of some of the risk-based approaches such as methods of handling exhaust ventilation, or wet methods to suppress dust through air filtration (213). However, in many small businesses, personal protective equipment may be the only option. Therefore, training and use of the appropriate and most up to date equipment is needed to properly select, fit-test, maintain, and wear whilst working, even in the phases of processing, storage, handling, or maintenance of materials or chemicals. It should be noted that failure to properly carry out any of these tasks may lead to failure of personal protective equipment to prevent further exposure.

9.1.3 Research recommendations and future directions

My thesis has identified future research gaps on aspects of occupational exposure and COPD. A summary of the research gaps including future research recommendations is presented below.

9.1.3.1 Exposure assessment using JEMs

One of the biggest challenges in population-based studies is to investigate occupational exposure adequately. Traditional approaches have been used for many years to assess occupational exposure and modified tools such as the ALOHA JEM are vital in estimating exposures for large-scale population-based studies. Future studies would benefit from further refinement of exposure for more quantitative exposure assessment similar to FINJEM (Finnish Job Exposure Matrix).

9.1.3.2 Lifetime work history calendar

The lifetime work history calendar including job title, job descriptions, and years worked, and hours worked per week is critical in occupational health research to capture the previous exposures as well as the length of employment. In my thesis, I used lifetime work

history calendar, but I did not use working hours because there was no adequate information on total working hours. Future health research with larger sample sizes should collect that information more adequately from the start of the study to avoid recall related biases by the participants.

9.1.3.3 Biological effects

Although there is an emerging body of literature suggesting an association between occupational exposures and COPD, the exact mechanism behind this relationship is less clear and has not yet been established. Therefore, future occupational health research targeted at elucidating the biological mechanisms of occupational exposure is essential. Understanding the biological mechanism will help to identify more accurate workplace exposure and development of new therapeutic strategies to prevent fixed type of AO at an early stage.

9.1.3.4 Genetic and epigenetic variations

Genetic and epigenetic variations may play a significant role in occupational exposure and subsequent development of COPD in offspring. Future research should focus on this issue and may need to investigate the role of genetics and epigenetics in the relationship between occupational exposure and COPD in offspring.

Finally, the age range in the TAHS cohort is the middle forties, and therefore they may not yet have developed moderate to severe fixed AO at this age. The sixth-decade follow-up of the TAHS cohort has just been completed and therefore the data are not available for analysis as yet. For this reason, I was unable to estimate the relevant associations for an older age group. Further investigation using the subsequent follow-up of this cohort on the incidence of fixed AO would be helpful to assess the actual impact of occupation related COPD within Australia.

9.2 Conclusions

During my doctoral work, I systematically synthesized and meta-analyzed the existing evidence around occupational exposures and COPD and chronic bronchitis in population-based studies. Subsequently using data from the TAHS, I attempted to address

limitations identified in the studies conducted to date. I critically investigated the association between occupational exposures and COPD as defined by fixed AO, chronic bronchitis, respiratory symptoms, and lung function decline. I also investigated effect modification by smoking, asthma and sex in these relationships. In summary, I have demonstrated the following:

- Occupational exposures to mineral dust and gases/fumes was associated with COPD; and mineral dust was associated with chronic bronchitis.
- Occupational exposures to pesticides and herbicides were associated with fixed AO, chronic bronchitis, and respiratory symptoms.
- Occupational exposures to biological dust, mineral dust, gases/fumes and VGDF were more significantly associated with fixed AO in non-asthmatics than asthmatics.
- Increasing cumulative exposure-unit years of exposure to chlorinated solvents were significantly associated with increased risks of fixed AO and gas transfer factor in women, but not in men.
- Occupational exposure to aromatic solvents was significantly associated with greater lung function decline.

Increasing cumulative EU-years of exposure to aromatic solvents was again significantly associated with greater lung function decline in women, than in men.

These results have filled some major research gaps in our understanding of the links between overall occupational exposures and COPD in the general population. The findings from my doctoral work also emphasize the need for future research on occupational exposures and lung health. I have confirmed in my study that occupational exposure to pesticides is a risk factor for COPD and newly identified occupational exposures to solvents and metals are also linked to increased risk of COPD. My finding of an association between pesticides and respiratory symptoms, and solvents and lung function decline further strengthens the assumption that occupational exposure is associated with an increased risk of

COPD. I have uncovered significant effect modification by asthma that indicates asthma is a major contributor to fixed AO at this age rather than particular occupational exposure. This finding emphasizes the need to utilize post-BD spirometry to define fixed AO which allows adequate consideration of asthma, especially for a middle-aged population. I also found increased risk of COPD in women which may lead to several recommendations including increased use of protective respiratory equipment, and workplace monitoring to reduce the level of exposure. By enhanced monitoring and use of protective equipment, the burden of COPD caused by occupational exposures has the potential to be substantially reduced.

References

1. Celli BR, Decramer M, Wedzicha JA, Wilson KC, Agustí A, Criner GJ, et al. An official American Thoracic Society/European Respiratory Society statement: research questions in COPD. Eur Respir J. 2015;45(4):879-905.

2. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Am J Respir Crit Care Med. 2017;195(5):557-82.

3. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. Lancet. 2015;385(9971):899-909.

4. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al. Changes in Forced Expiratory Volume in 1 Second over Time in COPD. N Engl J Med. 2011;365(13):1184-92.

5. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. Lancet. 2007;370:765–73.

6. Burney PGJ, Patel J, Newson R, Minelli C, Naghavi M. Global and regional trends in COPD mortality, 1990–2010. Eur Respir J. 2015;45(5):1239-47.

7. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.

8. AIHW. Chronic respiratory diseases in Australia: their prevalence, consequences and prevention [Internet]. Canberra, Australian Capital Territory: AIHW; 2005 [cited 11 August 2017]. Available from: http://www.aihw.gov.au/publication-detail/?id=6442467751.

9. AIHW. Mortality from asthma and COPD in Australia [Internet]. Canberra,Australian Capital Territory: AIHW; 2014 [cited 11 August 2017]. Available from: http://www.aihw.gov.au/publication-detail/?id=60129548233.

10. AIHW. Who gets COPD? [Internet] Canberra,Australian Capital Territory: AIHW; 2014 [cited 5 March 2017]. Available from: http://www.aihw.gov.au/copd/prevalence/.

11. Toelle B, Xuan W, Bird TE, Abramson MJ, Atkinson DN, Burton DL, et al. Respiratory symptoms and illness in older Australians: the Burden of Obstructive Lung Disease (BOLD) study. MJA. 2013;198(3):144-8.

12. Eisner MD, Anthonisen N, Coultas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An Official American Thoracic Society Public Policy Statement: Novel Risk Factors and the Global Burden of Chronic Obstructive Pulmonary Disease. Am J Resp Crit Care Med. 2010;182(5):693-718.

13. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. American Thoracic Society Statement: Occupational Contribution to the Burden of Airway Disease. Am J Resp Crit Care Med. 2003;167(5):787–97.

14. Hoy RF. Respiratory problems Occupational and environmental exposures. Australian family physician. 2012;41(11):856-60.

15. Cullinan P. Occupation and chronic obstructive pulmonary disease (COPD). Br Med Bull. 2012;104:143–61.

16. McGuire V, Nelson LM, Koepsell TD, Checkoway H, Longstreth WT, Jr. Assessment of occupational exposures in community-based case-control studies. Annu Rev Public Health. 1998;19:35-53.

17. Hoar SK, Morrison AS, Cole P, Silverman DT. An Occupation and Exposure Linkage System for the Study of Occupational Carcinogenesis. J Occup Med. 1980;22(11):722-26.

18. Kauppinen TP, Toikkanen J, Pukkala E. From Cross-Tabulations to Multipurpose Exposure Information Systems: A New Job-Exposure Matrix. Am J Ind Med. 1998;33(4):409-17.

19. Matheson MC, Benke G, Raven J, Sim MR, Kromhout H, Vermeulen R, et al. Biological dust exposure in the workplace is a risk factor for chronic obstructive pulmonary disease. Thorax. 2005;60(8):645–51.

20. Mehta AJ, Miedinger D, Keidel D, Bettschart R, Bircher A, Bridevaux PO, et al. Occupational exposure to dusts, gases, and fumes and incidence of chronic obstructive pulmonary diseases in the swiss cohort study on air pollution and lung and heart diseases in adults. Am J Resp Crit Care Med. 2012;185(12):1292-300.

21. Blanc PD, Iribarren C, Trupin L, Earnest G, Katz PP, Balmes J, et al. Occupational exposures and the risk of COPD: dusty trades revisited. Throax. 2009;64:6-12.

22. Trupin L, Earnest G, Pedro S, Balmes JR, Eisner MD, Yelin E, et al. The occupational burden of chronic obstructive pulmonary disease. Eur Respir J. 2003;22:462–9.

23. Heederik D, Kromhout H, Burema J, Biersteker K, Kromhout D. Occupational exposure and 25-year incidence rate of non-specific lung disease: the Zutphen Study. Int J Epidemiol. 1990;19(4):945-52.

24. Post WK, Heederik D, Kromhout H, Kromhout D. Occupational exposures estimated by a population specific job exposure matrix and 25 year incidence rate of chronic nonspecific lung disease (CNSLD): the Zutphen Study. Eur Respir J. 1994;7(6):1048-55.

25. Global Initiative For Asthma. Diagnosis of Diseases of Chronic Airflow Limitation: Asthma, COPD and Asthma-COPD Overlap Syndrome (ACOS). GINA; 2017. Available from: www.ginasthma.org.

26. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007;370(9589):741-50.

27. Barnes PJ. Sex Differences in Chronic Obstructive Pulmonary Disease Mechanisms. Am J Respir Crit Care Med. 2016;193(8):813-4.

28. Eng A, Mannetje At, McLean D, Ellison-Loschmann L, Cheng S, Pearce N. Gender differences in occupational exposure patterns. Occup Environ Med. 2011;68(12):888-94.

29. Matheson MC, Abramson MJ, Allen K, Benke G, Burgess JA, Dowty JG, et al. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). Int J Epidemiol. 2017;46(2):407-8i.

30. Office IL. International Standard Classification of Occupations: ISCO-88 [Internet]. Geneva, Switzerland; 1990 [updated 21 June 2016; cited 11 August 2017] [Available from: http://www.ilo.org/public/english/bureau/stat/isco/isco08/index.htm.

31. World Health Organization. The top 10 causes of death. Fact sheet N°310 [Internet]. Geneva; 2014 [updated January 2017; cited 11 August 2017]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.

32. Pauwels RA, Rabe KF. Burden and clinical features of chronic obstructive pulmonary disease (COPD). Lancet. 2004;364(9434):613-20.

33. Viegi G, Pedreschi M, Pistelli F, Di Pede F, Baldacci S, Carrozzi L, et al. Prevalence of airways obstruction in a general population: European Respiratory Society vs American Thoracic Society definition. Chest. 2000;117(5_suppl_2):339S-45S.

34. Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. Eur Respir J. 2003;22(2):268-73.

35. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: Systematic review and meta–analysis. J Glob Health. 2015;5(2):020415.

36. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J. 2006;28(3):523-32.

37. Menezes AM, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, Valdivia G, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. Lancet. 2005;366(9500):1875-81.

38. World Health Organization. Chronic Obstructive Pulmonary Disease (COPD): WHO Media centre 2017 [updated November 2016; cited 2016 2 August]. Available from: http://www.who.int/mediacentre/factsheets/fs315/en/.

39. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med. 2006;3(11):e442.

40. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

41. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23(6):932–46.

42. Sterk P. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J. 2004;23(4):497-98.

43. Thomsen M, Nordestgaard BG, Vestbo J, Lange P. Characteristics and outcomes of chronic obstructive pulmonary disease in never smokers in Denmark: a prospective population study. Lancet Respir Med. 2013;1(7):543-50.

44. Terzikhan N, Verhamme KM, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam Study. Eur J Epidemiol. 2016;31(8):785-92.

45. Quanjer PH, Pretto JJ, Brazzale DJ, Boros PW. Grading the severity of airways obstruction: new wine in new bottles. Eur Respir J. 2014;43(2):505-12.

46. Güder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP, et al. GOLD or lower limit of normal definition? a comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. Respir Res. 2012;13(1):13.

47. van Dijk W, Tan W, Li P, Guo B, Li S, Benedetti A, et al. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. Ann Fam Med. 2015;13(1):41-8.

48. Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

49. Vaz Fragoso CA, Concato J, McAvay G, Van Ness PH, Rochester CL, Yaggi HK, et al. The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2010;181(5):446-51.

50. Rennard SI, Drummond MB. Early chronic obstructive pulmonary disease: definition, assessment, and prevention. Lancet. 2015;385(9979):1778-88.

51. Johannessen A, Lehmann S, Omenaas ER, Eide GE, Bakke PS, Gulsvik A. Post-Bronchodilator Spirometry Reference Values in Adults and Implications for Disease Management. Am J Resp Crit Care Med. 2006;173(12):1316-25.

52. Cerveri I, Corsico A, Accordini S, Niniano R, Ansaldo E, Anto JM, et al. Underestimation of airflow obstruction among young adults using FEV1/FVC ,70% as a fixed cut-off: a longitudinal evaluation of clinical and functional outcomes. Thorax. 2008;63(12):1040–45.

53. Bhatt SP, Sieren JC, Dransfield MT, Washko GR, Newell JD, Jr., Stinson DS, et al. Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction. Thorax. 2014;69(5):409-14.

54. Alif S, Dharmage S, Bowatte G, Karahalios A, Benke G, Dennekamp M, et al. Occupational exposure and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analysis. Expert Rev Respir Med. 2016;10(8):861-72.

55. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Resp Crit Care Med. 2013;187(4):347-65.

56. Lopez AD, Mathers CD, Ezzati M, Jamison DT, CJL M. Global burden of disease and risk factors. Washington: The World Bank; 2006.
57. Berndt A, Leme AS, Shapiro SD. Emerging genetics of COPD. EMBO Mol Med. 2012;4(11):1144-55.
58. Pinkerton KE, Harbaugh M, Han MK, Jourdan Le Saux C, Van Winkle LS, Martin WJ, 2nd, et al. Women and Lung Disease. Sex Differences and Global Health Disparities. Am J Resp Crit Care Med. 2015;192(1):11-6.
59. Soriano JB, Davis KJ, Coleman B, Visick G, Mannino D, Pride NB. The proportional Venn diagram of obstructive lung disease: two approximations from the United States and the United Kingdom. Chest. 2003;124(2):474-81.
60. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med. 1998;339(17):1194-200.
61. Vonk JM, Jongepier H, Panhuysen CI, Schouten JP, Bleecker ER, Postma DS. Risk factors associated with the presence of irreversible airflow limitation and reduced transfer coefficient in patients with asthma after 26 years of follow up. Thorax. 2003;58(4):322-7.
62. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. Am Rev Respir Dis. 1987;136(1):62-8.
63. Tashkin DP, Altose MD, Connett JE, Kanner RE, Lee WW, Wise RA. Methacholine reactivity predicts changes in lung function over time in smokers with early chronic obstructive pulmonary disease. The Lung Health Study Research Group. Am J Resp Crit Care Med. 1996;153(6 Pt 1):1802-11.
64. Stuart BO. Deposition and clearance of inhaled particles. Environ Health Perspect. 1984;55:369-90.
65. Kromhout H, Vermeulen R. Application of job-exposure matrices in studies of the general population-some clues to their performance. Eur Respir Rev. 2001;11(80):80-90.
66. Keil U, Weiland SK, Birk T, Spelsberg A. Epidemiology of risks in the workplace. Soz Praventivmed. 1992;37(2):50-63.
67. Nordby KC, Noto H, Eduard W, Skogstad M, Fell AK, Thomassen Y, et al. Thoracic dust exposure is associated with lung function decline in cement production workers. Eur Respir J. 2016;48(2):331-9.

68. Torén K, Järvholm B. Effect of occupational exposure to vapors, gases, dusts, and fumes on copd mortality risk among swedish construction workers: A longitudinal cohort study. Chest 2014;145(5):992-7.

69. Eduard W, Pearce N, Douwes J. Chronic bronchitis, COPD, and lung function in farmers: the role of biological agents. Chest. 2009;136(3):716-25.

70. Christiani DC, Wang X-R, Pan L-d, Zhang H-X, Sun B-X, Dai H, et al. Longitudinal changes in pulmonary function and respiratory symptoms in cotton textile workers: a 15-yr follow-up study. Am J Resp Crit Care Med. 2001;163(4):847-53.

71. Szklo M. Population-based cohort studies. Epidemiol Rev. 1998;20(1):81-90.

72. Tielemans E, Heederik D, Burdorf A, Vermeulen R, Veulemans H, Kromhout H, et al. Assessment of occupational exposures in a general population: comparison of different methods. Occup Environ Med. 1999;56(3):145–51.

73. Goldberg M, Hemon D. Occupational epidemiology and assessment of exposure. Int J Epidemiol. 1993;22 Suppl 2:S5-9.

74. Benke G, Sim M, Fritschi L, Aldred G, Forbes A, Kauppinen T. Comparison of occupational exposure using three different methods: hygiene panel, job exposure matrix (JEM), and self reports. Appl Occup Environ Hyg. 2001;16(1):84-91.

75. Stewart WF, Stewart PA. Occupational case-control studies: I. Collecting information on work histories and work-related exposures. Am J Ind Med. 1994;26(3):297-312.

76. Stengel B, Pisani P, Limasset JC, Bouyer J, Berrino F, Hemon D. Retrospective evaluation of occupational exposure to organic solvents: questionnaire and job exposure matrix. Int J Epidemiol. 1993;22 Suppl 2:S72-82.

77. Siemiatycki J, Dewar R, Richardson L. Costs and statistical power associated with five methods of collecting occupation exposure information for population-based case-control studies. Am J Epidemiol. 1989;130(6):1236-46.

78. Kauppinen TP. Assessment of exposure in occupational epidemiology. Scand J Work Environ Health. 1994;20(Spec No):19-29.

79. Unied Nations. International Standard Industrial Classification of All Economic Activities (ISIC) New York, [Internet].UN2016 [updated 2017; cited 11 August 2017]. Available from: https://unstats.un.org/unsd/cr/registry/regcst.asp?Cl=27.

80. Lavoue´ J, Pintos J, Tongeren M, Kincl L, Richardson L, Kauppinen T, et al. Comparison of exposure estimates in the Finnish job-exposure matrix FINJEM with a JEM derived from expert assessments performed in Montreal. Occup Environ Med. 2012;69:465-71.

81. Sim M, Benke G. AusJEM - Australian Job Exposure Matrix Australia: Monash University; 2012 [Available from: http://www.coeh.monash.org/ausjem.html.

82. Kauppinen TP, Mutanen PO, Seitsamo JT. Magnitude of misclassification bias when using a job-exposure matrix. Scand J Work Environ Health. 1992;18(2):105-12.

83. Sunyer J, Kogevinas M, Kromhout H, Anto´ JM, Roca J, Tobias A, et al. Pulmonary Ventilatory Defects and Occupational Exposures in a Population-based Study in Spain. Am J Resp Crit Care Med. 1998;157(2):512–17.

84. Sunyer J, Zock JP, Kromhout H, Esteban RG, Radon K, Jarvis D, et al. Lung Function Decline, Chronic Bronchitis, and Occupational Exposures in Young Adults. Am J Resp Crit Care Med. 2005;172(9):1139–45.

85. de Jong K, Boezen H, Kromhout H, Vermeulen R, Postma D, Vonk J, et al. Pesticides and other occupational exposures are associated with airway obstruction: the LifeLines cohort study. Occup Environ Med. 2014;71(2):88-96.

86. Hoppin JA, Tolbert PE, Flagg EW, Blair A, Zahm SH. Use of a life events calendar approach to elicit occupational history from farmers. Am J Ind Med. 1998;34(5):470-6.

87. Porcellato L, Carmichael F, Hulme C. Using occupational history calendars to capture lengthy and complex working lives: a mixed method approach with older people. Int J Soc Res Meth. 2014:1-18.

88. Engel LS, Keifer MC, Zahm SH. Comparison of a traditional questionnaire with an icon/calendar-based questionnaire to assess occupational history. Am J Ind Med. 2001;40(5):502-11.

89. Zahm SH, Colt JS, Engel LS, Keifer MC, Alvarado AJ, Burau K, et al. Development of a life events/icon calendar questionnaire to ascertain occupational histories and other characteristics of migrant farmworkers. Am J Ind Med. 2001;40(5):490-501.

90. de Jong K, Boezen HM, Kromhout H, Vermeulen R, Postma DS, Vonk JM. Association of occupational pesticide exposure with accelerated longitudinal decline in lung function. Am J Epidemiol. 2014;179(11):1323-30.

91. Hoppin JA. Pesticides and respiratory health: where do we go from here? Occup Environ Med. 2014;71(2):80.

92. Benke G, Sim MR, McKenzie DP, Macfarlane E, Del Monaco A, Hoving JL, et al. Comparison of first, last, and longest-held jobs as surrogates for all jobs in estimating cumulative exposure in cross-sectional studies of work-related asthma. Ann Epidemiol. 2008;18(1):23-7.

93. Douwes J, Thorne P, Pearce N, Heederik D. Bioaerosol health effects and exposure assessment: progress and prospects. Ann Occup Hyg. 2003;47(3):187-200.

94. Spurzem JR, Romberger DJ, Von Essen SG. Agricultural lung disease. Clin Chest Med. 2002;23(4):795-810.

95. Dutkiewicz J, Jabionski L, Olenchock SA. Occupational Biohazards: A Review. Am J Ind Med. 1988;14(5):605-23.

96. Dalphin JC, Bildstein F, Pernet D, Dubiez A, Depierre A. Prevalence of chronic bronchitis and respiratory function in a group of dairy farmers in the French Doubs province. Chest. 1989;95(6):1244-7.

97. Monso E, Riu E, Radon K, Magarolas R, Danuser B, Iversen M, et al. Chronic obstructive pulmonary disease in never-smoking animal farmers working inside confinement buildings. Am J Ind Med. 2004;46(4):357-62.

98. Lam KBH, Yin P, Jiang CQ, Zhang WS, Adab P, Miller MR, et al. Past dust and GAS/FUME exposure and COPD in Chinese: the Guangzhou Biobank Cohort Study. Respir Med. 2012;106(10):1421-8.

99. Korn RJ, Dockery DW, Speizer FE, Ware JH, Ferris BG. Occupational Exposures and Chronic Respiratory Symptoms: A Population-Based Study. Am Rev Respir Dis. 1987;136(2):298-304.

100. LeVan TD, Koh WP, Lee HP, Koh D, Yu MC, London SJ. Vapor, dust, and smoke exposure in relation to adult-onset asthma and chronic respiratory symptoms: the Singapore Chinese Health Study. Am J Epidemiol. 2006;163(12):1118-28.

101. Suadicani P, Hein HO, Meyer HW, Gyntelberg F. Exposure to cold and draught, alcohol consumption, and the NS-phenotype are associated with chronic bronchitis: an epidemiological investigation of 3387 men aged 53-75 years: the Copenhagen Male Study. Occup Environ Med. 2001;58(3):160-4.

102. Heederik D, Pouwels H, Kromhout H, Kromhout D. Chronic non-specific lung disease and occupational exposures estimated by means of a job exposure matrix: the Zutphen Study. Int J Epidemiol. 1989;18(2):382-9.

103. Hansell A, Ghosh RE, Poole S, Zock JP, Weatherall M, Vermeulen R, et al. Occupational Risk Factors for Chronic Respiratory Disease in a New Zealand Population Using Lifetime Occupational History. J Occup Environ Med. 2014;56(3):270-80.

104. Dijkstra AE, De Jong K, Boezen HM, Kromhout H, Vermeulen R, Groen HJM, et al. Risk factors for chronic mucus hypersecretion in individuals with and without COPD: Influence of smoking and job exposure on CMH. Occup Environ Med. 2014;71(5):346-52.

105. Krstev S, Ji BT, Shu XO, Gao YT, Blair A, Lubin J, et al. Occupation and chronic bronchitis among Chinese women. J Occup Environ Med. 2008;50(1):64-71.

106. de Meer G, Kerkhof M, Kromhout H, Schouten J, Heederik D. Interaction of atopy and smoking on respiratory effects of occupational dust exposure: a general population-based study. Environ Health. 2004;3(1):6.

107. Skorge TD, Eagan TML, Eide GE, Gulsvik A, Bakke PS. Occupational exposure and incidence of respiratory disorders in a general population. Scand J Work Environ Health. 2009;35(6):454–60.

108. Würtz ET, Schlunssen V, Malling TH, Hansen JG, Omland O. Occupational COPD among Danish never-smokers: a population-based study. Occup Environ Med. 2015;72(6):456-9.

109. Würtz ET, Schlünssen V, Malling TH, Hansen JG, Omland Ø. Occupational Chronic Obstructive Pulmonary Disease in a Danish Population-Based Study. Copd. 2015;12(4):435-43.

110. Tagiyeva N, Sadhra S, Mohammed N, Fielding S, Devereux G, Teo E, et al. Occupational airborne exposure in relation to Chronic Obstructive Pulmonary Disease (COPD) and lung function in individuals without childhood wheezing illness: A 50-year cohort study. Environ Res. 2017;153:126-34.

111. Tegen I, Schepanski K. The global distribution of mineral dust. IOP Conference Series: Earth and Environmental Science. 2009;7(1):012001.

112. Hochgatterer K, Moshammer H, Haluza D. Dust Is in the Air: Effects of Occupational Exposure to Mineral Dust on Lung Function in a 9-year Study. Lung. 2013;191(3):257-63.

113. Ould-Kadi F, Nawrot TS, Hoet PH, Nemery B. Respiratory function and bronchial responsiveness among industrial workers exposed to different classes of occupational agents: a study from Algeria. J Occup Med Toxicol. 2007;2:11.

114. Brüske I, Thiering E, Heinrich J, Huster K, Nowak D. Biopersistent Granular Dust and Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta- Analysis. PLoS One. 2013;8(11):1-10.

115. Santo Tomas LH. Emphysema and chronic obstructive pulmonary disease in coal miners. Curr Opin Pulm Med. 2011;17(2):123-5.

116. Cockcroft A, Seal RM, Wagner JC, Lyons JP, Ryder R, Andersson N. Post-mortem study of emphysema in coalworkers and non-coalworkers. Lancet. 1982;2(8298):600-3.

117. Becklake MR, Irwig L, Kielkowski D, Webster I, de Beer M, Landau S. The predictors of emphysema in South African gold miners. Am Rev Respir Dis. 1987;135(6):1234-41.

118. Hnizdo E, Sluis-Cremer GK, Abramowitz JA. Emphysema type in relation to silica dust exposure in South African gold miners. Am Rev Respir Dis. 1991;143(6):1241-7.

119. Becklake MR. Chronic airflow limitation: its relationship to work in dusty occupations. Chest. 1985;88(4):608-17.

120. Caplan-Shaw CE, Yee H, Rogers L, Abraham JL, Parsia SS, Naidich DP, et al. Lung pathologic findings in a local residential and working community exposed to World Trade Center dust, gas, and fumes. J Occup Environ Med. 2011;53(9):981-91.

121. Rom WN, Reibman J, Rogers L, Weiden MD, Oppenheimer B, Berger K, et al. Emerging exposures and respiratory health: World Trade Center dust. Proc Am Thorac Soc. 2010;7(2):142-5.

122. Summer W, Haponik E. Inhalation of irritant gases. Clin Chest Med. 1981;2(2):273-87.

123. Das R, Blanc PD. Chlorine gas exposure and the lung: a review. Toxicology and industrial health. 1993;9(3):439-55.

124. Patil LRS, Smith RG, Vorwald AJ, Mooney TF. The Health of Diaphragm Cell Workers Exposed to Chlorine. Am Ind Hyg Assoc J. 1970;31(6):678-86.

125. do Pico GA. Hazardous exposure and lung disease among farm workers. Clin Chest Med. 1992;13(2):311-28.

126. Johnsen HL, Hetland SM, Benth JS, Kongerud J, Søyseth V. Dust Exposure Assessed by a Job Exposure Matrix Is Associated with Increased Annual Decline in FEV1 A 5-year Prospective Study of Employees in Norwegian Smelters. Am J Resp Crit Care Med. 2010;181:1234–40.

127. Fishwick D, Bradshaw LM, D'Souza W, Town IAN, Armstrong R, Pearce N, et al. Chronic Bronchitis, Shortness of Breath, and Airway Obstruction by Occupation in New Zealand. Am J Resp Crit Care Med. 1997;156(5):1440-46.

128. Xu X, Christiani DC, Dockery DW, Wang L. Exposure—Response Relationships between Occupational Exposures and Chronic Respiratory Illness: A Community-based Study. Am Rev Respir Dis. 1992;146(2):413-8.

129. Darby A, Waterhouse JC, Stevens V, Billings CG, Billings CG, Burton CM, et al. Chronic obstructive pulmonary disease among residents of an historically industrialised area. Throax. 2012;67:901-7.

130. Lange P, Parner J, Prescott E, Vestbo J. Chronic bronchitis in an elderly population. Age and ageing. 2003;32(6):636-42.

131. Zock JP, Sunyer J, Kogevinas M, Kromhout H, Burney P, Antó JM. Occupation, Chronic Bronchitis, and Lung Function in Young Adults An International Study. Am J Resp Crit Care Med. 2001;163(7):1572–7.

132. Hagstad S, Backman H, Bjerg A, Ekerljung L, Ye X, Hedman L, et al. Prevalence and risk factors of COPD among never-smokers in two areas of Sweden–occupational exposure to gas, dust or fumes is an important risk factor. Respir Med. 2015;109(11):1439-45.

133. Jaén Á, Zock JP, Kogevinas M, Ferrer A, Marín A. Occupation, smoking, and chronic obstructive respiratory disorders: A cross sectional study in an industrial area of Catalonia, Spain. Environ Health. 2006;5(2).

134. Ye M, Beach J, Martin JW, Senthilselvan A. Occupational pesticide exposures and respiratory health. Int J Environ Res Public Health. 2013;10(12):6442-71.

135. Mamane A, Baldi I, Tessier J-F, Raherison C, Bouvier G. Occupational exposure to pesticides and respiratory health. Eur Respir Rev. 2015;24(136):306-19.

136. Doust E, Ayres JG, Devereux G, Dick F, Crawford JO, Cowie H, et al. Is pesticide exposure a cause of obstructive airways disease? Eur Respir Rev. 2014;23(132):180-92.

137. Jomichen J, El-Zaemey S, Heyworth JS, Carey RN, Darcey E, Reid A, et al. Australian work exposures studies: occupational exposure to pesticides. Occup Environ Med. 2016.
138. Shirangi A, Fritschi L, Holman CD. Prevalence of occupational exposures and protective practices in Australian female veterinarians. Aust Vet J. 2007;85(1-2):32-8.
139. Zuskin E, Mustajbegovic J, Schachter EN, Kern J, Deckovic-Vukres V, Trosic I, et al. Respiratory function in pesticide workers. J Occup Environ Med. 2008;50(11):1299-305.
140. Sprince NL, Lewis MQ, Whitten PS, Reynolds SJ, Zwerling C. Respiratory symptoms: associations with pesticides, silos, and animal confinement in the Iowa Farm Family Health and Hazard Surveillance Project. Am J Ind Med. 2000;38(4):455-62.
141. Hashemi N, Mirsadraee M, Shakeri MT, Varasteh AR. Prevalence of work-related respiratory symptoms in Iranian farmers. Can Respir J. 2006;13(4):198-202.
142. Wilkins JR, 3rd, Engelhardt HL, Rublaitus SM, Crawford JM, Fisher JL, Bean TL. Prevalence of chronic respiratory symptoms among Ohio cash grain farmers. Am J Ind Med. 1999;35(2):150-63.
143. Negatu B, Kromhout H, Mekonnen Y, Vermeulen R. Occupational pesticide exposure and respiratory health: a large-scale cross-sectional study in three commercial farming systems in Ethiopia. Thorax. 2016.
144. Chakraborty S, Mukherjee S, Roychoudhury S, Siddique S, Lahiri T, Ray MR. Chronic exposures to cholinesterase-inhibiting pesticides adversely affect respiratory health of agricultural workers in India. J Occup Health. 2009;51(6):488-97.
145. Faria NMX, Facchini LA, Fassa AG, Tomasi E. Pesticides and respiratory symptoms among farmers. Rev Saude Publica. 2005;39(6):973-81.
146. Hoppin JA, Valcin M, Henneberger PK, Kullman GJ, Umbach DM, London SJ, et al. Pesticide use and chronic bronchitis among farmers in the agricultural health study. Am J Ind Med. 2007;50(12):969-79.
147. Schenker MB, Stoecklin M, Lee K, Lupercio R, Zeballos RJ, Enright P, et al. Pulmonary function and exercise-associated changes with chronic low-level paraquat exposure. Am J Resp Crit Care Med. 2004;170(7):773-9.

148. Neta G, Stewart PA, Rajaraman P, Hein MJ, Waters MA, Purdue MP, et al. Occupational exposure to chlorinated solvents and risks of glioma and meningioma in adults. Occup Environ Med. 2012;69(11):793-801.

149. Vizcaya D, Christensen KY, Lavoue J, Siemiatycki J. Risk of lung cancer associated with six types of chlorinated solvents: results from two case-control studies in Montreal, Canada. Occup Environ Med. 2013;70(2):81-5.

150. Schenker MB, Jacobs JA. Respiratory effects of organic solvent exposure. Tubercle and lung disease : the official journal of the International Union against Tuber Lung Dis. 1996;77(1):4-18.

151. Mattei F, Guida F, Matrat M, Cenee S, Cyr D, Sanchez M, et al. Exposure to chlorinated solvents and lung cancer: results of the ICARE study. Occup Environ Med. 2014;71(10):681-9.

152. Ebbehoj NE, Hein HO, Suadicani P, Gyntelberg F. Occupational organic solvent exposure, smoking, and prevalence of chronic bronchitis-an epidemiological study of 3387 men. J Occup Environ Med. 2008;50(7):730-5.

153. Lebowitz MD. Occupational exposures in relation to symptomatology and lung function in a community population. Environ Res. 1977;14(1):59-67.

154. Le Moual N, Orlowski E, Schenker MB, Avignon M, Brochard P, Kauffmann F. Occupational exposures estimated by means of job exposure matrices in relation to lung function in the PAARC survey. Occup Environ Med. 1995;52(10):634-43.

155. Hamzah NA, Mohd Tamrin SB, Ismail NH. Metal dust exposure and lung function deterioration among steel workers: an exposure-response relationship. Int J Occup Environ Health. 2016;22(3):224-32.

156. Ulvestad B, Bakke B, Eduard W, Kongerud J, Lund MB. Cumulative exposure to dust causes accelerated decline in lung function in tunnel workers. Occup Environ Med. 2001;58(10):663-9.

157. Rehfisch P, Anderson M, Berg P, Lampa E, Nordling Y, Svartengren M, et al. Lung function and respiratory symptoms in hard metal workers exposed to cobalt. J Occup Environ Med. 2012;54(4):409-13.

158. Szram J, Schofield SJ, Cosgrove MP, Cullinan P. Welding, longitudinal lung function decline and chronic respiratory symptoms: a systematic review of cohort studies. Eur Respir J. 2013;42(5):1186-93.

159. Luttrell WE, Giles CB. Toxic tips: Osmium tetroxide. J Ch Healt S. 2007;14(5):40-1.

160. Rondini EA, Walters DM, Bauer AK. Vanadium pentoxide induces pulmonary inflammation and tumor promotion in a strain-dependent manner. Part Fibre Toxicol. 2010;7:9.

161. Kiviluoto M. Observations on the lungs of vanadium workers. Br J Ind Med. 1980;37(4):363-6.

162. Bernard A. Cadmium & its adverse effects on human health. Indian J Med Res. 2008;128(4):557-64.

163. Rubio ML, Sanchez-Cifuentes MV, Peces-Barba G, Verbanck S, Paiva M, Gonzalez Mangado N. Intrapulmonary gas mixing in panacinar- and centriacinar-induced emphysema in rats. Am J Respir Crit Care Med. 1998;157(1):237-45.

164. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. In: Luch A, editor. Molecular, Clinical and Environmental Toxicology. Volume 3: Environmental Toxicology. 3rd ed. Berlin, Germany: Springer 2012. p. 133-64.

165. Mehta AJ, Thun GA, Imboden M, Ferrarotti I, Keidel D, Künzli N, et al. Interactions between SERPINA1 PiMZ genotype, occupational exposure and lung function decline. Occup Environ Med. 2014;71(4):234-40.

166. Liao SY, Lin X, Christiani DC. Occupational exposures and longitudinal lung function decline. Am J Ind Med. 2015;58(1):14-20.

167. Harber P, Tashkin DP, Simmons M, Crawford L, Hnizdo E, Connett J. Effect of occupational exposures on decline of lung function in early chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;176(10):994-1000.

168. Humerfelt S, Gulsvik A, Skjrerven A, Nilssen S, Kvale G, Sulheim O, et al. Decline in FEV1 and airflow limitation related to occupational exposures in men of an urban community. Eur Respir J. 1993;6:1095-103.

169. Krzyzanowski M, Jedrychowski W, Wysocki M. Factors associated with the change in ventilatory function and the development of chronic obstructive pulmonary disease in a

13-year follow-up of the Cracow Study. Risk of chronic obstructive pulmonary disease. Am Rev Respir Dis. 1986;134(5):1011-9.

170. Lindberg A, Jonsson A-C, Ronmark E, Lundgren R, Larsson L-G, Lundback B. Ten-year cumulative incidence of COPD and risk factors for incident disease in a symptomatic cohort. Chest 2005;127(5):1544-52.

171. Sansores RH, Ramírez-Venegas A. COPD in women: susceptibility or vulnerability? Eur Respir J. 2016;47(1):19-22.

172. Kennedy SM, Chambers R, Du W, Dimich-Ward H. Environmental and occupational exposures: do they affect chronic obstructive pulmonary disease differently in women and men? Proc Am Thorac Soc. 2007;4(8):692-4.

173. Hnizdo E, Sullivan PA, Bang KM, Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: A study of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2002;156(8):738-46.

174. Le Moual N, Bakke P, Orolowski E, Heederik D, Kromhout H, Kennedy SM, et al. Performance of Population specific Job Exposure Matrices (JEMs): European collaborative analysis on occupational risk factors for chronic obstructive pulmonary disease with job exposure martices (ECOJEM). Occup Environ Med. 2000;57(2):126-32.

175. Abramson MJ, Perret JL, Dharmage SC, McDonald VM, McDonald CF. Distinguishing adult-onset asthma from COPD: a review and a new approach. Int J Chron Obstruct Pulmon Dis. 2014;9:945-62.

176. Alif S, Dharmage S, Karahalios A, Bowatte G, Benke G, Dennekamp M, et al. Occupational exposures and risk of Chronic Obstructive Pulmonary Disease: a systematic review and meta-analyses. The Thoracic Society of Australia & New Zealand (TSANZ) ASM; Gold Coast, Queensland, Australia: Respirology; 2015. p. 75 TP035.

177. Wharton C, Dharmage SC, Jenkins MA, Dite G, Hopper J, Giles GG, et al. Tracing 8,600 participants 36 years after recruitment at age seven for the Tasmanian Asthma Study. Aust N Z J Public Health. 2006;30(2):105-10.

178. Gibson H, Silverstone H, Gandevia B, Hall G. Respiratory disorders in seven-year old children in Tasmania-Aims, methods and administration of the survey. Med J Aust. 1969;2(4):201-5.

179. Rathnayake RK, Tang MLK, Simpson JA, Burgess JA, Mészáros D, Feather I, et al. Adult Serum Cytokine Concentrations and the Persistence of Asthma. Int Arch Allergy Immunol. 2013;161:342-50.

180. Macintyre N, Crapo R, Viegi G, Johnson D, Van Der Grinten C, Brusasco V, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26(4):720-35.

181. Wanger J, Clausen J, Coates A, Pedersen O, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26(3):511-22.

182. Roca J, Rodriguez-Roisin R, Cobo E, Burgos F, Perez J, Clausen JL. Single-breath carbon monoxide diffusing capacity prediction equations from a Mediterranean population. Am Rev Respir Dis. 1990;141(4 Pt 1):1026-32.

183. Thompson BR, Johns DP, Bailey M, Raven J, Walters EH, Abramson MJ. Prediction equations for single breath diffusing capacity (TlCO) in a middle aged caucasian population. Thorax. 2008;63(10):889-93.

184. Lambert A, Drummond MB, Wei C, Irvin C, Kaminsky D, McCormack M, et al. Diagnostic accuracy of FEV 1/forced vital capacity ratio z scores in asthmatic patients. J Allergy Clin Immunol. 2015;136(3):649-53.

185. Textor J, Hardt J, Knüppel S. DAGitty: A Graphical Tool for Analyzing Causal Diagrams. Epidemiology. 2011;22(5):745-51.

186. Australian Bureau of Statistics. Socio-Economic Indexes for Areas (SEIFA) Technical Paper. Canberra.:Commonwealth of Australia; 2011. ABS Catalogue no. 2033.0.55.001; 2011.

187. Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret JL, et al. Occupational exposure to pesticides are associated with fixed airflow obstruction in middle-age. Thorax. 2017. Epub ahead of print.

188. Alif SM, Dharmage SC, Benke G, Dennekamp M, Burgess JA, Perret JL, et al. Lifetime occupational exposure to vapor, gases/fumes, dust and risk of COPD at 45 years: the tasmanian longitudinal health study (TAHS). American Thoracic Society Annual Conference 2016; San Francisco, California, USA: Am J Respir Crit Care Med; 2016. p. A2989.

189. Rapaport L. Occupational pesticide and herbicide exposure tied to lung disease. Reuters. 2017 29 July 2017 (col. 2017).

190. Alif S, Dharmage S, Benke G, Dennekamp M, Burgess JA, Perret JL, et al. Occupational exposures to solvents and metals are associated with fixed airflow obstruction. Scand J Work Environ Health. 2017. Epub ahead of print.

191. Cakmak S, Dales RE, Liu L, Kauri LM, Lemieux CL, Hebbern C, et al. Residential exposure to volatile organic compounds and lung function: results from a population-based cross-sectional survey. Environ Pollut. 2014;194:145-51.

192. Ben-Zaken Cohen S, Pare PD, Man SF, Sin DD. The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism. Am J Respir Crit Care Med. 2007;176(2):113-20.

193. Sin DD, Cohen SB, Day A, Coxson H, Pare PD. Understanding the biological differences in susceptibility to chronic obstructive pulmonary disease between men and women. Proc Am Thorac Soc. 2007;4(8):671-4.

194. Lilley RC, Cryer PC, Firth HM, Herbison GP, Feyer AM. Ascertainment of occupational histories in the working population: the occupational history calendar approach. Am J Ind Med. 2011;54(1):21-31.

195. Zock JP, Cavalle N, Kromhout H, Kennedy SM, Sunyer J, Jaen A, et al. Evaluation of specific occupational asthma risks in a community-based study with special reference to single and multiple exposures. J Expo Anal Environ Epidemiol. 2004;14(5):397-403.

196. Kennedy SM, Le Moual N, Choudat D, Kauffmann F. Development of an asthma specific job exposure matrix and its application in the epidemiological study of genetics and environment in asthma (EGEA). Occup Environ Med. 2000;57:635–41.

197. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med. 2004;350(10):1005-12.

198. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.

199. Perret JL, Dharmage SC, Matheson MC, Johns DP, Gurrin LC, Burgess JA, et al. The Interplay between the Effects of Lifetime Asthma, Smoking, and Atopy on Fixed Airflow Obstruction in Middle Age. Am J Resp Crit Care Med. 2013;187(1):42-8.

200. de Marco R, Accordini S, Marcon A, Cerveri I, Antó JM, Gislason T, et al. Risk Factors for Chronic Obstructive Pulmonary Disease in a European Cohort of Young Adults. Am J Resp Crit Care Med. 2011;183(7):891-7.

201. Marcon A, Anto JM, Cerveri I, Gislason T, Heinrich J, Janson C, et al. Can we use pre-bronchodilator spirometry to define post-bronchodilator airflow obstruction? Eur Respir J. 2015;46(suppl 59).

202. Silva GE, Sherrill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. Chest. 2004;126(1):59-65.

203. McGeachie MJ. Childhood asthma is a risk factor for the development of chronic obstructive pulmonary disease. Curr Opin Allergy Clin Immunol. 2017;17(2):104-9.

204. Butland BK, Ghosh RE, Strachan DP, Cullinan P, Jarvis D. Job choice and the influence of prior asthma and hay fever. Occup Environ Med. 2011;68:494-501.

205. Richiardi L, Barone-Adesi F, Merletti F, Pearce N. Using directed acyclic graphs to consider adjustment for socioeconomic status in occupational cancer studies. J Epidemiol Community Health. 2008;62(7):e14.

206. Brisson C, Loomis D, Pearce N. Is social class standardisation appropriate in occupational studies? J Epide Com H. 1987;41(4):290-4.

207. Hill AB. The environment and disease: association or causation? 1965. J R Soc Med. 2015;108(1):32-7.

208. COPD case finding in community settings [Internet]. Lung Foundation Australia. 2016 [cited 11 August 2017]. Available from: http://lungfoundation.com.au/wp-content/uploads/2014/02/Position-Paper-1.pdf.

209. Pesticide health risk assessments [Internet]. Victoria, Australia: Department of Health and Human Services, State Government of Victoria, Australia; 2015 [updated 2017; cited 11 August 2017]. Available from: https://www2.health.vic.gov.au/public-health/environmental-health/pesticide-use-and-pest-control/pesticides-safe-use/pesticide-health-risk-assessments.

210. Department of Health and Human Services, State Government of Victoria. Guidelines for the safe use of pesticides in non-agricultural workplaces [Internet]. In: Rural and Regional Health and Aged Care Services Division VG, Department of Human Services, , editor. Melbourne, Victoria: State Government of Victoria; 2007 [updated 2017;

cited 11 August 2017]. Available from: https://www2.health.vic.gov.au/about/publications/policiesandguidelines/guidelines-for-safe-use-pesticides-non-agricultural-workplaces.

211. World Health Organization. Public health impact of pesticides used in agriculture. Geneva, Switzerland: World Health Organization; 1990.

212. Work Safe Victoria. A health and safety self-assessment checklist for small business [Internet]. Victoria, Australia Safework Australia 2013 [updated 2017; cited 11 August 2017]. Available from: https://www.worksafe.vic.gov.au/documents.

213. Fishwick D, Sen D, Barber C, Bradshaw L, Robinson E, Sumner J, et al. Occupational chronic obstructive pulmonary disease: a standard of care. Occup Med (Lond). 2015;65(4):270-82.

Appendices

Appendix 1- The TAHS 1968 baseline study questionnaire

TAS. 10/P.1

TASMANIAN ASTHMA SURVEY

CHILD'S MEDICAL HISTORY — CONFIDENTIAL

THIS SECTION IS FOR OFFICE USE ONLY

Code

1 Survey Number

CHILD'S SURNAME CALLARY

CHILD'S CHRISTIAN NAME Bernadette

SCHOOL HEALTH NUMBER HCK 092
(not to be coded)

Sex F

145 ~~155~~ ~~145~~ School Name ~~BURNIE~~ Montello 155

108 ~~111~~ ~~108~~ Child's School Number 111

TO BE FILLED IN BY PARENT, GUARDIAN OR RELATIVE

Important

(a) Before completing this form, please indicate your relationship to the child named in the panel above by putting a cross in the appropriate square below:

MOTHER	FATHER	STEP-PARENT OR ADOPTED PARENT OR GUARDIAN	OTHER RELATION	NO RELATION
[X] 1	[ ] 2	[ ] 3	[ ] 4	[ ] 5

(b) Has the child named above got a twin, or any brothers or sisters born in the same year (that is 1961)? (put a cross in the appropriate square) YES [ ] NO [X]

If the answer is YES, please give Christian names and the name of the school the brother or sister attends:

Name.....

School.....

(c) Please state the number of living full brothers and sisters in the family (excluding any born in 1961). Nil

(d) If you do not read English well and have difficulty understanding the questions for this reason, please put a cross here [ ]

(e) Please name the local doctor or hospital usually attended by this child for any ailment.

TB Clinic Medical Centre

HOW TO ANSWER THE QUESTIONS:

In most cases, unless otherwise indicated, you are asked to answer YES or NO by putting a cross [X] in the appropriate square. Sometimes, if the answer is not simply YES or NO, there are more than two squares provided, but you should still put a cross in only one of the several squares. Only three questions (relating to months of the year) may need a cross in more than one square, but these exceptions are specifically mentioned.

Please make sure that **ALL** questions are answered; please do not omit one, as this might mean we can not use the other information you will have given us. We understand that the answers to some questions can only be approximate, just as we understand that one's memory cannot always be perfectly accurate. If you wish to add more information or more details, please do so on a separate sheet of paper. Do **NOT** write extra notes on the form, and always answer the question with a cross in the most appropriate square, even if you add extra notes on a separate piece of paper.

Note that there are really four separate forms — the first deals with the health of the child named in the panel above, the second deals with the health of the mother, the third with the health of the father, and the fourth with the health of brothers and sisters. All these are equally important in helping us to understand the importance of the whole family in respiratory and allergic illnesses.

Office use only

1. (a) Where was he/she born?

Tasmania	[X] 1
Other Australian State	[ ] 2
United Kingdom, New Zealand, South Africa, Canada, United States of America	[ ] 3
Other Overseas country (Please Name.....)	[ ] 4

(b) Date of birth 22-7-61

1 2

2. Did he/she have infantile (baby) eczema? YES ☐ NO ☒

3. Has he/she ever had eczema in the creases (bends) of elbows, wrists, or knees? ☐ ☒

4. How was he/she fed in the first three months of life?
   - Breast only ☐ 1
   - Bottle only ☒ 2
   - Breast and bottle ☐ 3

5. Does he/she have a stutter or stammer? YES ☐ NO ☒

6. Has he/she a habit of biting the fingernails? ☐ ☒

7. During the first three years of life did you have to take the child to the doctor because of difficulties with feeding?
   - Often ☒ 1
   - Occasionally ☐ 2
   - Never ☐ 3

8. For how much time in the last twelve months has the child been confined to the house because of chest illnesses?
   - Not at all ☐ 1
   - One to seven days ☐ 2
   - Eight to thirty days ☒ 3
   - More than a month ☐ 4

9. Has he/she had the tonsils removed? YES ☒ NO ☐

10. Has he/she had **more** than two sore throats or attacks of tonsilitis in the past twelve months? ☐ ☒

11. Have you ever been told by a doctor that he/she had pneumonia or pleurisy?
   - No, Never ☐ 1
   - Yes, Once or twice ☐ 2
   - Yes, More than twice ☒ 3

12. Have you been told by a doctor that he/she is allergic to any foods or medicines? YES ☒ NO ☐

13. Does he/she get hives?
   - Never ☐ 1
   - Once or twice a year ☐ 2
   - More than twice a year ☒ 3

14. Has he/she **at any time** in his/her life suffered from attacks of asthma or of wheezy breathing?
   (**Note:** Please regard "asthma" and "wheezy breathing" as being much the same thing for this survey; we do not ask you to try to tell the difference) YES ☐ NO ☒

The following questions (Nos. 15 to 21) relate to the details of these illnesses, and need to be answered if the answer to question 14 was YES. If the answer to question 14 was NO, omit these questions, and go on to question 21.

15. How long is it since the last attack?
   - Less than a month ago 1 ☐
   - Over one but less than three months ago 2 ☐
   - Over three but less than six months ago 3 ☐
   - Over six but less than twelve months ago 4 ☐
   - Over one year but less than two years ago 5 ☐
   - Over two years ago 6 ☐

16. On the average (as near as you can say), how often do these attacks tend to occur over the last two years or so?
   - About once in twenty-four hours 1 ☐
   - About once a week 2 ☐
   - About once a fortnight 3 ☐
   - About once a month 4 ☐

NO ☒

About once every three months 5 ☐
About once every six months 6 ☐
About once a year (or less often) 7 ☐
No attacks at all in the last two years 8 ☐

17. On the average (as near as you can say), how long do these attacks usually last (with usual treatment)?

NO ☒

Less than twelve hours 1 ☐
A day or so 2 ☐
A week or so 3 ☐
A month or so 4 ☐
"Continuous" (never free of asthma or wheezing for more than a day or two) 5 ☐

18. At what age did these attacks begin?

Under 1 year 1 ☐
Over 1 and under 2 years 2 ☐
Over 2 and under 3 years 3 ☐
Over 3 and under 4 years 4 ☐
Over 4 and under 5 years 5 ☐
Over 5 and under 6 years 6 ☐
Over 6 and under 7 years 7 ☐
Over 7 years 8 ☐

19. Since the attacks began, approximately how many has he/she had altogether

NO ☐

One attack only 1 ☐
Two to five attacks 2 ☐
Six to ten attacks 3 ☐
Eleven to twenty attacks 4 ☐
Over twenty attacks 5 ☐

20. If the attacks tend to be more frequent or more severe at any particular time of the year, indicate the "bad" months by putting a cross in the appropriate square(s) (but DO NOT put a cross against more than FOUR of the twelve months). If no month is worse than the others, leave all squares blank.

NO ☐

JAN.	FEB.	MCH.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

→ 21. Has he/she **at any time** in his/her life suffered from attacks of bronchitis or attacks of cough with sputum (phlegm) in the chest ("loose" or "rattly" cough)?

(**Note:** Please regard "bronchitis" and "cough with sputum (phlegm) in the chest," and "loose or rattly cough" as being much the same thing for this survey; we do not ask you to try to tell the difference).

YES ☒ NO ☐

NO ☒

The following questions (Nos. 22-27) relate to the details of these illnesses, and need to be answered if the answer to question 21 was YES. If the answer to question 21 was NO, omit these questions and go on to question 28.

22. How long is it since the last attack?

Less than a month ago ☐ 1
Over one but less than three months ago ☐ 2
Over three but less than six months ago ☒ 3
Over six but less than twelve months ago ☐ 4
Over one year but less than two years ago ☐ 5
Over two years ago ☐ 6

23. On the average (as near as you can say) how often do these attacks tend to occur over the last two years or so?

About once in twenty-four hours ☐
About once a week ☐
About once a fortnight ☐
About once a month ☒
About once every three months ☐
About once every six months ☐
About once a year (or less often) ☐
No attacks at all in the last two years ☐

24. On the average (as near as you can say), how long do these attacks usually last (with usual treatment)?

Less than twelve hours	☐ 1
A day or so	☐ 2
A week or so	☒ 3
A month or so	☐ 4
"Continuous" (never free of loose cough for more than a day or two)	☐ 5

25. At what age did these attacks begin?

Under one year	☒ 1
Over 1 and under 2 years	☐ 2
Over 2 and under 3 years	☐ 3
Over 3 and under 4 years	☐ 4
Over 4 and under 5 years	☐ 5
Over 5 and under 6 years	☐ 6
Over 6 and under 7 years	☐ 7
Over 7 years	☐ 8

26. Since the attacks began, approximately how many has he/she had altogether?

One attack only	☐ 1
Two to five attacks	☐ 2
Six to ten attacks	☐ 3
Eleven to twenty attacks	☐ 4
Over twenty attacks	☒ 5

27. If the attacks tend to be more frequent or more severe at any particular time of the year, indicate the "bad" months by putting a cross in the appropriate square(s) (but DO NOT put a cross against more than FOUR of the twelve months). If no month is worse than the others, leave all squares blank.

JAN.	FEB.	MCH.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
☒	☐	☐	☐	☐	☒	☒	☐	☐	☐	☐	☒

28. Does he/she get attacks of "hay fever" (that is, sneezing, running or blocked nose, sometimes with itchy eyes or nose)? YES ☒ NO ☐

If the answer to question 28 is NO, omit question 29.

29. If these hay fever attacks tend to be more frequent or more severe at any particular time of the year, indicate the "bad" months by putting a cross in the appropriate square(s) (but DO NOT put a cross against more than FOUR of the twelve months). If no month is worse than another, leave all squares blank.

JAN.	FEB.	MCH.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
☒	☒	☒	☐	☐	☐	☐	☒	☒	☒	☐	☐

30. Is he/she prone to "colds in the head" (that is, more than two or three colds a year)? YES ☐ NO ☒

If the answer to question 30 is NO, omit question 31.

31. If these head colds tend to be more frequent or more severe at any particular time of the year, indicate the "bad" months by putting a cross in the appropriate square(s) (but DO NOT put a cross against more than FOUR of the twelve months). If no month is worse than another, leave all the squares blank.

JAN.	FEB.	MCH.	APRIL	MAY	JUNE	JULY	AUG.	SEPT.	OCT.	NOV.	DEC.
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

32. Has he/she ever had a chest X-ray? YES ☒ NO ☐

If the answer is YES:

Where was the X-ray taken? Royal Hobart Hospital
(Name of hospital, doctor or clinic)

What year was it taken? 19 66

Was it normal, as far as you know? YES ☒ NO ☐

33. Has he/she ever attended a chest clinic as a contact of a person with tuberculosis? YES ☐ NO ☒

Please check your answers to all the questions: Thank you.

MERCURY 67-4866

Appendix 2- The TAHS 2002 follow-up postal survey questionnaire

UNIVERSITY OF TASMANIA

MONASH University

WINDOW

THE UNIVERSITY OF MELBOURNE

The Fourth Follow-up Study of the 1968 Tasmanian Asthma Survey

We would like to invite you to take part in a postal survey for a follow-up study of the 1968 Tasmanian Asthma Survey. In 1968, as part of a statewide survey of all 7 year old children, your parents filled in a questionnaire about your health. They also completed surveys for your brothers and sisters as well as for themselves. With 45,900 Tasmanians involved, this research is the largest asthma study in the world.

This current follow-up study will look at the factors that affect respiratory health in adults. We have found your address on the federal electoral rolls *(allowed under sections 91(4A)(e) and 91(2A)(c) of the Commonwealth Electoral Act 1918 and Regulation 10 of the Electoral and Referendum Regulations)* or recently from your brothers or sisters.

We would be grateful if you could help us by completing this survey booklet and returning it in the reply paid envelope provided. We'd like as many of you to complete the survey booklet as possible, **even if you do not have any asthma or any respiratory problems**. This is so we can compare information from people with and without respiratory illnesses to identify the causes of these conditions. This survey booklet contains:

- **Consent Form** which you need to sign if you agree to fill in this survey booklet
- **Respiratory Health Questionnaire**
- **Family Contact Details Form**

We are asking for the details of your family so we can also survey them with a similar questionnaire in the future. Providing their details does not commit them to be involved in this study. You may wish to discuss this with them to make sure they are happy for you to pass on their information. A lot of time has gone by since the original study and if this letter happens to bring up memories of upsetting events that have occurred in your family, we sincerely apologise.

If you have questions about this research or need help in completing the survey, please contact Cathryn Wharton on **1800 110 711** (free call Australia wide) or email: inq-tas@unimelb.edu.au Alternatively, you could contact the chief investigator Dr Shyamali Dharmage on (03) 8344 0737.

Your participation in this survey is completely voluntary. If you do not wish to take part you are not obliged to, but please let us know by ringing 1800 110 711 (free call) so we do not send you a reminder letter. All information you provide is strictly confidential. Your Consent Form (page 2) and Family Contact Details Form (pages 11 and 12) which have your identifying information will be removed from this booklet and stored separately from your questionnaire. If you have a complaint about this project or concerns about your rights as a research participant, you can contact the Executive Officer, Human Research Ethics, The University of Melbourne on (03) 8344 4071.

Over the years this study has made many great contributions to the understanding of respiratory illnesses. Thank you for your help with this research so far and for taking the time to consider our request.

Sincere regards,

Dr Shyamali Dharmage, Senior Lecturer
Chief Investigator of the T.A.S.

Cathryn Wharton, Senior Research Assistant
Project Coordinator of the T.A.S.

RESPIRATORY HEALTH QUESTIONNAIRE
TASMANIAN ASTHMA STUDY 1968 - 2003/04

Mail-out 1

Please read these instructions & examples before you fill in the questionnaire.

- Please do not fold or bend this booklet.



- Please use a blue or black pen or 2B pencil.
- Please mark your responses like this: ○ ● ○ ○
- Ovals must be completely shaded in.
- Cross out any mistakes and shade in the correct oval, e.g: ○ ⊗ ○ ● ○
- If you need help to answer any of the questions please contact us on 1800 110 711 (free call).
- Unless indicated, shade in only one oval

Example: To indicate "female"

Ⓐ Male
● Female

- Where a number is required, write the number in the boxes and shade in the ovals.

Example: To indicate "2"



Write number AND shade in ovals

Today's Date:

Day		Month	Year
		○ JAN	○ 2003
		○ FEB	○ 2004
0	0	○ MAR	○ 2005
1	1	○ APR	○ 2006
2	2	○ MAY	○ 2007
3	3	○ JUN	
	4	○ JUL	
	5	○ AUG	
	6	○ SEP	
	7	○ OCT	
	8	○ NOV	
	9	○ DEC	

Your date of birth:

If this is **NOT CORRECT**, please record your date of birth below:

Day		Month	Year		Write number AND shade in ovals
		○ JAN	19		
		○ FEB			
0	0	○ MAR		0	0
1	1	○ APR		1	1
2	2	○ MAY		2	2
3	3	○ JUN		3	3
	4	○ JUL		4	4
	5	○ AUG		5	5
	6	○ SEP		6	6
	7	○ OCT		7	7
	8	○ NOV		8	8
	9	○ DEC		9	9

HEALTH QUESTIONS

1. Have you ever been allergic to any of the following?
   SHADE ALL THAT APPLY
   - ○ Foods
   - ○ Medicine
   - ○ Dust
   - ○ Animals
   - ○ Pollen, grass, trees or flowers

2. Have you ever had eczema or any kind of skin allergy?
   - ○ No
   - ○ Yes

3. Have you ever had hay fever (that is sneezing, running or blocked nose *when you **do not** have a cold or the flu*)?
   - ○ No
   - ○ Yes

4. Have you had treatment for heart trouble in the past 10 years?
   - ○ No
   - ○ Yes

BARCODE & ID NUMBER TO BE PRINTED HERE

5. Are you disabled from walking by a condition other than heart or lung disease?

- ○ No
- ○ Yes

6. Are you troubled by shortness of breath when hurrying on level ground or walking up a slight hill?

- ○ No → go to question 7
- ○ Yes → continue

6.1 Do you have to walk slower than people of your age because of breathlessness?

- ○ No
- ○ Yes

6.2 Do you have to stop for breath when walking at your own pace on level ground?

- ○ No
- ○ Yes

6.3 Do you ever get short of breath when resting?

- ○ No
- ○ Yes

7. Do you **usually** cough when you **do not** have a cold?

- ○ No → go to question 8
- ○ Yes → continue

7.1 Are there months in which you cough on most days?

- ○ No → go to question 8
- ○ Yes → continue

7.1.1 Do you cough on most days for at least three months of each year?

- ○ No
- ○ Yes

7.1.2 For how many years have you had this cough?

- ○ Less than 2 years
- ○ 2 - 5 years
- ○ More than 5 years

8. Do you **usually** have phlegm in your chest when you **do not** have a cold?

- ○ No → go to question 9
- ○ Yes → continue

8.1 Are there months in which you have phlegm in your chest on most days?

- ○ No → go to question 9
- ○ Yes → continue

8.1.1 Do you bring up this phlegm on most days for at least three months each year?

- ○ No
- ○ Yes

8.1.2 For how many years have you had this phlegm?

- ○ Less than 2 years
- ○ 2 - 5 years
- ○ More than 5 years

9. Have you, **at any time in your life**, suffered from **cough with phlegm** in the chest (with or without a cold)?

- ○ No → go to question 10
- ○ Yes → continue

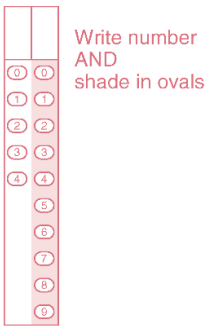
9.1 Have you had cough with phlegm on most days for at least three months of each year for two successive years?

- ○ No
- ○ Yes

10. Have you, **at any time in your life**, suffered from attacks of asthma or wheezy breathing? (Regard asthma and wheezy breathing as being much the same for this question.)

- ○ No → go to question 13
- ○ Yes → continue

10.1 At what age did these attacks begin? *(age in years)*



10.2 How long ago did you have the last attack?

- ○ Within the last year
- ○ Over 1 year but less than 2 years ago
- ○ Over 2 years ago

11. Are you:

- ○ Male → go to question **13**
- ○ Female → continue

11.1 Have you ever noticed that your asthma changes with your monthly menstrual period?
SHADE ONE ONLY

- ○ No, my asthma does not change when I have my period
- ○ Yes, my asthma gets worse when I have my period
- ○ Yes, my asthma gets better when I have my period
- ○ I don't have periods
- ○ Don't know

12. Have you been pregnant since you first had asthma?

- ○ No → go to question **13**
- ○ Yes → continue

12.1 What happened to your asthma during your pregnancies?
SHADE ONE ONLY

- ○ Improved
- ○ Got worse
- ○ Stayed the same
- ○ Not the same for all pregnancies
- ○ Don't know

→ go to question **13**

Please answer A, B and C for questions 13 to 16.

	A. Has a doctor ever told you that you have or had this condition?	**B.** How old were you when you were told you had this condition? *(age in years)* Write number AND shade in ovals (Eg. 2 years: 0 2)	**C.** Have you taken any medicine (including inhalers or tablets) for this condition in the **last three months**?
13. Asthma?	○ No → go to question **14** ○ Yes → continue		○ No ○ Yes
14. Chronic bronchitis?	○ No → go to question **15** ○ Yes → continue		○ No ○ Yes
15. Emphysema?	○ No → go to question **16** ○ Yes → continue		○ No ○ Yes
16. Chronic obstructive pulmonary disease or chronic obstructive airways disease?	○ No → go to question **17** ○ Yes → continue		○ No ○ Yes

17. Have you had wheezing or whistling in your chest **in the last 12 months**? (wheezing means a whistling sound, however high or low pitched and however faint.)

- ○ No → go to question **18**
- ○ Yes → continue

17.1 Have you been at all breathless when the wheezing noise was present?

- ○ No
- ○ Yes

17.2 Have you had this wheezing or whistling when you **did not** have a cold?

- ○ No
- ○ Yes

18. Have you, at any time **in the last 12 months**, woken up with a feeling of tightness in your chest?

- ○ No
- ○ Yes

19. Have you, at any time **in the last 12 months**, been woken at night by an attack of shortness of breath?

- ○ No
- ○ Yes

YOURSELF, WORK AND HOME

Now, we are asking for some information about yourself, your work and home to look at the effect of these things on people's respiratory health.

20. In your lifetime, have you smoked at least 100 cigarettes or equal amounts of cigars, pipes, or any other tobacco product?

- ○ No → go to question **21**
- ○ Yes → continue

20.1 How old were you when you started smoking?
(age in years)

Write number AND shade in ovals

20.2 Do you currently smoke (within the last 4 weeks)?

- ○ Not at all → go to question **20.3**
- ○ Yes, daily → continue
- ○ Yes, at least weekly → continue
- ○ Yes, less than weekly → continue

20.2.1 On average, how much do you **currently** smoke (total number of cigarettes or equivalent product)? (Provide the average number per day **OR** per week **OR** per month)

per day **OR** per week **OR** per month

Write number AND shade in ovals

→ go to question **21**

20.3 How old were you when you stopped smoking?
(age in years)

Write number AND shade in ovals

20.3.1 On average, during periods when you smoked, how much **did** you smoke (total number of cigarettes or equivalent product)? (Provide the average number per day **OR** per week **OR** per month)

per day **OR** per week **OR** per month

Write number AND shade in ovals

21. Not counting yourself, how many people in your household currently smoke regularly (most days of the week) inside the house?

Write number AND shade in ovals

22. Do people smoke regularly (most days of the week) in the room where you work (not counting yourself)?

- ○ No
- ○ Yes

23. On average, how many hours per day are you exposed to other people's tobacco smoke (work and home)?

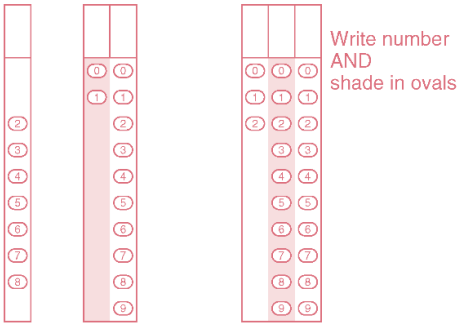
Write number AND shade in ovals



24. What is your height without shoes? (answer either in feet and inches **OR** in centimetres.)

Feet and Inches **OR** Centimetres

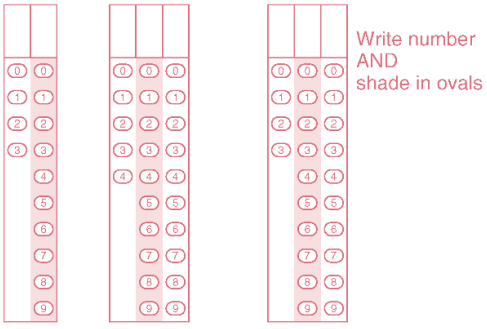
Write number AND shade in ovals



25. What is your weight? (answer either in stone and pounds **OR** in pounds **OR** in kilograms)?

Stone and Pounds **OR** Kilograms

Write number AND shade in ovals



26. How many of your own (biological) children have you had?

Write number AND shade in ovals



If you have not had children → go to question **27**
If you have had children ⟶ continue

26.1 How many of your own (biological) children have ever suffered from attacks of asthma or wheezy breathing?

Write number AND shade in ovals



27. What is the highest educational or vocational qualification that you have completed?

SHADE ONE ONLY

- ○ Grade 1 to 6
- ○ Grade 7 to 9
- ○ Grade 10 or 11
- ○ Grade 12 or equivalent (eg. Higher School Certificate)
- ○ Trade / Apprenticeship (eg. Hairdresser, electrician, plumber etc)
- ○ Certificate or Diploma (eg. Child care, technician etc)
- ○ University degree (eg. Bachelor)
- ○ Higher University Degree (eg. Graduate Diploma, Masters, PhD)

28. Are you currently employed or self-employed?
SHADE ONE ONLY

- ○ Yes
- ○ No, I am currently studying.
- ○ No, unemployed for less than 6 months and actively seeking work
- ○ No, unemployed for more than 6 months and actively seeking work
- ○ No, I am not working due to health, family or other reasons
- ○ No, retired
- ○ No, other

29. What is your main occupation?
SHADE ONE ONLY

- ○ Manager or administrator (eg. magistrate, general manager, school principal, director of nursing, farm manager)
- ○ Professional (eg. scientist, doctor, nurse, allied health professional, teacher, artist)
- ○ Associate professional (eg. technician, manager, youth worker, police officer)
- ○ Tradesperson or related worker (eg. hairdresser, gardener, florist)
- ○ Advanced clerical or service worker (secretary,flight attendant, law clerk, personal assistant)
- ○ Intermediate clerical, sales or service worker (eg. typist, data entry operator, receptionist, child care worker, nursing assistant, hospitality worker)
- ○ Intermediate production or transport worker (eg. machine operator, bus driver, sewing machinist)
- ○ Elementary clerical, sales or service worker (eg. filing/mail clerk, parking inspector, sales assistant, telemarketer, housekeeper)
- ○ Labourer or related worker (cleaner, factory worker, farm hand, kitchen hand)
- ○ House person

30. Which types of heating do you use at home?
SHADE ALL THAT APPLY

- ○ Gas ducted central heating
- ○ Coal or wood fire
- ○ Gas room heater
- ○ Electric heater (eg. radiator, fan or Dimplex-type)
- ○ Other central heating (eg. electric, hydronic, slab floor heating)
- ○ Reverse cycle air-conditioning
- ○ Other

31. What kind of stove do you **mostly** use for **cooking**?
SHADE ONE ONLY

- ○ Gas
- ○ Electric
- ○ Coal, coke or wood
- ○ Other

32. Do you have an exhaust fan over the stove?

- ○ No → go to question 33
- ○ Yes → continue

32.1 When cooking how often do you use the fan?

- ○ All of the time
- ○ Some of the time
- ○ None of the time

32.2 Does the fan take the fumes outside the house?

- ○ No
- ○ Yes
- ○ Don't know

33. Has there ever been mould or mildew on any surfaces, other than food, in your home?

- ○ No → go to instructions on bottom of page
- ○ Yes → continue

33.1 Which rooms have been affected?
SHADE ALL THAT APPLY

- ○ Bathrooms
- ○ Your bedroom
- ○ Other bedrooms
- ○ Living areas
- ○ Kitchen
- ○ Any other area/s

33.2 Has there been mould or mildew on any surface, other than food, in your home **in the last 12 months**?

- ○ No
- ○ Yes

***If you are male**, please make sure you have signed the Consent Form (page 2) and completed the Family Contact Details Form (pages 11 & 12). Please return this whole booklet in the reply paid envelope provided. Thank you for your time and contribution to the T.A.S.*

***If you are female**, please go to the next page.*

SUPPLEMENT FOR WOMEN

We are looking at the reasons why more women have asthma than men, especially since it is more common in boys than in girls. This is why we are asking the following questions. Thank you for your help.

34. Have you ever had a menstrual period?

- ○ No → go to question **35**
- ○ Yes → continue

34.1 What was the age of your first period? *(age in years)*

Write number AND shade in ovals



35. Have you **ever** used birth control pills or other hormonal contraceptives (implants or injections)?

- ○ No → go to question **36**
- ○ Yes → continue

35.1 At what age did you first use birth control pills or other hormonal contraceptives? *(age in years)*

Write number AND shade in ovals



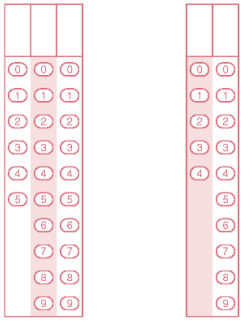
35.2 Are you currently taking birth control pills or other hormonal contraceptives?

- ○ No
- ○ Yes

35.3 Over your whole lifetime, in total how many months or years have you taken birth control pills or other hormonal contraceptives? (answer in months **OR** years.)

Write number AND shade in ovals

Months **OR** Years



36. Are you currently pregnant?

- ○ No
- ○ Yes
- ○ Don't know

37. Have you ever been pregnant in the past?

- ○ No → go to instructions below
- ○ Yes → go to question **38** (next page)

If No, please make sure that you have signed the Consent Form (page 2) and completed the Family Contact Details Form (pages 11 and 12). Please return this whole booklet in the reply paid envelope provided.
Thank you for your time and contribution to the T.A.S.

38. For each of your past pregnancies (including live births, miscarriages, abortions or still births), please fill in the following information going down the page. If more than 8 pregnancies, please record the details on a separate piece of paper.

	1st pregnancy	2nd pregnancy	3rd pregnancy	4th pregnancy	5th pregnancy	6th pregnancy	7th pregnancy	8th pregnancy
38.1 What was your age when you became pregnant? *(age in years)* Write number AND shade in ovals								
38.2 Taking 40 **weeks** as the usual length, how long was this pregnancy (counting from your last menstrual period)? Write number AND shade in ovals	Don't know ○	Don't know ○	Don't know ○	Don't know ○	Don't know ○	Don't know ○	Don't know ○	Don't know ○
38.3 Was this a live birth? (i.e not a miscarriage, abortion or stillbirth?)	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes
38.4 IF LIVEBIRTH, did you breast-feed the baby or express breast milk for your baby?	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes	○ No ○ Yes
38.5 IF BREASTFED, for how many **months** did you breastfeed or express breast milk? Write number AND shade in ovals								

Now please make sure that you have signed the Consent Form (page 2) and completed the Family Contact Details Form (pages 11 & 12). Please return this whole booklet in the reply paid envelope provided.
Thank you for your time and contribution to the T.A.S.

The Fourth Follow-up Study of the 1968 Tasmanian Asthma Survey

FAMILY CONTACT DETAILS FORM

We would like to collect the contact details of your family so we can also survey them with a similar questionnaire in the future. Providing their information does not commit them to be involved. You may wish to discuss this with them to make sure they are happy with you passing on their information.

ALL NAMES AND ADDRESSES ARE KEPT STRICTLY CONFIDENTIAL

If you have any questions about this research, contact Cathryn Wharton on 1800 110 711. Please DO NOT separate this page from your booklet. Thank you!

Main study participant details:

Your name: *Family ID:* *ID:*

If this is not correct please provide your current name below:

Current name:

Your address:

If this is not correct please provide your correct address below:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: *Work Ph:* *Mobile Ph:*

Details of your parents:

Name: *ID:*

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: *Work Ph:* *Mobile Ph:*

Name: *ID:*

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: *Work Ph:* *Mobile Ph:*

Details of your brothers and sisters:

Name: *ID:*

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: *Work Ph:* *Mobile Ph:*

Name: *ID:*

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: *Work Ph:* *Mobile Ph:*

Name: *ID:*

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: *Work Ph:* *Mobile Ph:*

Please continue to back page

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Name: ID:

If this is not correct please provide current name below:

Current name:

Address:

Street number *Street name* *Suburb* *Postcode*

Home Ph: Work Ph: Mobile Ph:

Thank you for completing these details.

Do not fold this booklet or remove any of the pages. Please post this completed booklet in the reply paid envelope provided or mail to:

Tasmanian Asthma Study
Department of Public Health
The University of Melbourne
Reply Paid 75370
CARLTON VIC 3053

Appendix 3- The TAHS 2004 laboratory study questionnaire

Participant ID: ____

Appointment date: ____ *day month year*

Participant initials: ____

Centre number: ____

Participant DOB: ____ *day month year*

Investigator initials: ____

Sample number: 1

(Centre number: Royal Hobart Hospital= 1, Northern Lung Function Service= 2, Burnie Physiology= 3, Alfred Hospital= 4)

For questions where the subject has to choose one answer, read out the question and all the categories before expecting them to respond. Definitions of ambiguous terms are given in text boxes. To standardise the questionnaire administration across centres, avoid providing any further explanation other than what is given in the questionnaire.

HOME ENVIRONMENT

First I am going to ask few questions about your home and the area where you live.

1. For how many years have you lived in your present home? ☐☐ *(<1 year code as 1)*

2. In which decade was your present home built?

Tick one ☑

- ❒ Before 1940
- ❒ 1941-1960
- ❒ 1961-1970
- ❒ 1971-1980
- ❒ 1981-1990
- ❒ 1990- Present
- ❒ Don't know

3. What is the base structure of your home?

Tick one

- ❒ Concrete slab
- ❒ Stumps and wooden flooring
- ❒ Combination of above
- ❒ Don't know

4. How old is the mattress in your bed?

Tick one

- ❒ Less than 12 months old
- ❒ 1-5 years old
- ❒ More than 5 years old
- ❒ Don't know
- ❒ Not relevant (e.g. waterbed)

5. Is there fitted carpet in the bedroom? ❒ No ❒ Yes

If Yes ☞ 5.1 What is the age of the carpet? *Tick one*

- ❒ Less than 12 months old
- ❒ 1 - 5 years old
- ❒ More than 5 years old
- ❒ Don't know

6. On average, how often is your bedroom vacuumed, or if it has a hard floor, how often is it swept or mopped? *Tick one*

- ❒ 5 or more times each week
- ❒ 2 - 4 times each week
- ❒ Once a week
- ❒ Less than once a week but more than once a month
- ❒ Once a month or less

7. On average, how often is your bedroom aired by opening windows for at least for 1-hour? *Tick one*

- ❒ 5 or more times each week
- ❒ 2-4 times each week
- ❒ Once a week
- ❒ Less than once a week but more than once a month
- ❒ Once a month or less

8. Do you keep or own any cats? ❒ No ❒ Yes

If no, go to Q9

If yes ☞ 8.1 How many? Number ☐☐

8.2 Are the cats **allowed** indoors? ❒ No ❒ Yes

If no, go to Q10

If yes ☞ 8.2.1 Are the cats **allowed** in the bedroom? ❒ No ❒ Yes

Now go to Q10

9. Has there been a cat in the house in the last 12 months? ❒ No ❒ Yes ❒ Don't know

AIR POLLUTION

10. During working days (Monday to Friday) is the traffic noise at home so intense that you would have to close the windows so you are not disturbed?

Tick one

- ❒ Constantly
- ❒ Frequently
- ❒ Seldom
- ❒ Never
- ❒ Don't know (never at home during BH)

11. During working days (Monday to Friday), how often do heavy vehicles such as trucks or buses pass your house?

Tick one

- ❒ Constantly
- ❒ Frequently
- ❒ Seldom
- ❒ Never
- ❒ Don't know (never at home during BH)

12. On a scale of 0 to 10, how much is **the area where you live** subjected to woodsmoke in winter? Zero means not at all and 10 means severely affected. *Number* ☐☐

13. On a scale of 0 to 10, how much is **the area where you live** subjected to fog or smog in winter? Zero means not at all and 10 means severely affected. *Number* ☐☐

14. On a scale of 0 to 10, when you are at home, how much are you annoyed by outdoor air pollution from traffic, industry, woodsmoke or other sources if you keep the windows open? Zero means no annoyance and 10 means intolerable annoyance. *Number* ☐☐

Definitions to be used when administering the questions below:

"Attack" or "flare up" of asthma: is a period of time when asthma symptoms are worse or more frequent than usual. One could have asthma symptoms regularly or intermittently without getting attacks or flare-ups. The attacks tend to occur after a cold/sore throat or during an 'allergen season'.

Chronic Bronchitis/COPD/COAD/emphysema: cough and sputum for at least 3 months for 2 successive years.

ASTHMA

Now I am going to ask few questions about few respiratory conditions that you may or may not have.

15. Have you ever had asthma? ❒ No ❒ Yes

If no, go to Q16 page 7

If yes continue

15.1 Was this confirmed by a doctor? ❒ No ❒ Yes

If yes 15.2 How old were you when this was confirmed? ☐☐ *years old*

15.3 How old were you when you had your most recent symptoms of asthma? ☐☐ *years old*

Symptom Severity

15.4. Have you been woken from your sleep by your asthma?

last 12 months		*last 1 month*	
❒ No	❒ Yes	❒ No	❒ Yes

If Yes to last month:

15.4.1 How many nights were you woken from sleep by your asthma in the last week? ☐☐ *Number of nights*

15.5. Have you had asthma symptoms when you wake in the morning?

last 12 months		*last 1 month*	
❒ No	❒ Yes	❒ No	❒ Yes

If Yes to last month:

15.5.1 How many mornings in the last week? ☐☐ *Number of mornings*

15.6 Have you been limited in any of the following activities because of asthma?

Tick the appropriate boxes in each category:	*last 12 months*		*last 1 month*	
15.6.1 All activities	❒ No	❒ Yes	❒ No	❒ Yes
15.6.2 When dressing	❒ No	❒ Yes	❒ No	❒ Yes
15.6.3 Walking on level ground	❒ No	❒ Yes	❒ No	❒ Yes

		last 12 months		last month	
15.6.4	Hurrying on level ground	❒ No	❒ Yes	❒ No	❒ Yes
15.6.5	Walking up stairs or up hills	❒ No	❒ Yes	❒ No	❒ Yes
15.6.6	Active sports	❒ No	❒ Yes	❒ No	❒ Yes
15.6.7	Other (Specify) _____	❒ No	❒ Yes	❒ No	❒ Yes

☞ *If Yes to any of 15.6.1 to 15.6.7, go to 15.7. If all were No, do 15.6.8 first.*

15.6.8 Would you agree or disagree with the following statement:

	last 12 months		last month	
"My asthma has not limited any of my activities."	❒ agree	❒ disagree	❒ agree	❒ disagree

15.7. How frequent have your asthma symptoms (of any severity) been?

Tick one

- ❒ No asthma in the past 12 months
- ❒ Asthma symptoms in the past 12 months but not in the last month
- ❒ Asthma symptoms in the last month, but not frequent (less than once per week)
- ❒ Frequent (once per week or more but not daily) in the last 1 month
- ❒ Persistent (daily)

☞ *If 'No asthma in the past 12 months', go to Q15.14. If any asthma in last 12 months continue*

15.8. How frequent have your asthma attacks/flare ups been over the past 12 months?

An "attack" or "flare up" of asthma is a period of time when asthma symptoms are worse or more frequent than usual. One could have asthma symptoms regularly or intermittently without getting attacks or flare-ups.

Tick one

- ❒ None in the past 12 months
- ❒ 3 or less in the past 12 months
- ❒ 4 or more but less than monthly
- ❒ More than monthly in the last 12 months
- ❒ More than weekly or persistent
- ❒ Not sure

15.9. Have you had an episode of asthma which has made you unable to speak or severe enough to limit your speech to only 1 or 2 words between breaths?

	last 12 months		last 1 month	
	❒ No	❒ Yes	❒ No	❒ Yes

15.10. On average, how would **you** rate the severity of your asthma?

	last 12 months tick one	*last 1 month tick one*
Not severe at all	❒	❒
Mild	❒	❒
Moderate	❒	❒
Severe	❒	❒
Not sure	❒	❒

Events

15.11. Have you lost any days from work, school or usual activities because of your asthma?

	last 12 months		*last 1 month*	
	❒ No	❒ Yes	❒ No	❒ Yes
If yes ☞: 15.11.1. How many?				
	last 12 months		*last 1 month*	

15.12. Have you had an attack or symptoms of asthma that was so bad, you needed to call your general practitioner, ambulance, emergency locum or 24 hour clinic?

	last 12 months		*last 1 month*	
	❒ No	❒ Yes	❒ No	❒ Yes
If yes ☞ 15.12.1. How many?				
	last 12 months		*last 1 month*	

15.13. Have you had an attack or symptoms of asthma that was so bad you had to go to a hospital emergency or casualty department?

	last 12 months		*last 1 month*	
	❒ No	❒ Yes	❒ No	❒ Yes
If yes ☞ 15.13.1. How many?				
	last 12 months		*last 1 month*	

15.14. Have you ever been admitted to a hospital because of your asthma? ❒ No ❒ Yes

If no, go to Q16

If yes ☞ 15.14.1 In the past 12 months? ❒ No ❒ Yes

If yes ☞ 15.14.1.1 How many times in the last 12 months? ☐☐
Number

15.14.1.2 How many times in the last 1 month? ☐☐
Number

15.15. Have you ever had an attack or symptoms of asthma which resulted in an admission to a hospital intensive care unit? ❒ No ❒ Yes

COPD/COAD/Chronic Bronchitis/EMPHYSEMA

16. Have you ever had Chronic Obstructive Pulmonary Disease/Chronic Obstructive Airways Disease/Chronic Bronchitis/Emphysema?
Signs of these illnesses are cough and sputum for at least 3 months for 2 years in a row.

❒ No ❒ Yes

If no, go to Q17

If yes continue

16.1 Was this confirmed by a doctor? ❒ No ❒ Yes

If yes ☞ 16.2 How old were you when this was confirmed? ☐☐ *years old*

FAMILY PREDISPOSITION

Interviewers note: Encourage respondents to give answers to the best of their knowledge. Don't read out the "Don't Know' option, and avoid using it whenever possible. If they don't know the health status of all of their siblings (or children), record their answers for the ones they do know about. If they don't know about any of their siblings (or children), then use 'Don't Know.'

I am now going to ask about the respiratory conditions of your family members. It is possible that you are not aware of these details but respond according to what you know about your family.

17. Has your biological mother ever had self reported or doctor diagnosed:

17.1 Asthma? ❒ No ❒ Yes ❒ Don't know

17.2 COPD, COAD, chronic bronchitis or emphysema? ❒ No ❒ Yes ❒ Don't know

18. Has your biological father ever had self reported or doctor diagnosed:

18.1 Asthma? ❒ No ❒ Yes ❒ Don't know

18.2 COPD, COAD, chronic bronchitis or emphysema? ❒ No ❒ Yes ❒ Don't know

19. Do you, or did you, have any biological brothers or sisters? ❒ No ❒ Yes ❒ Don't know
This includes half-brothers and half-sisters, but not step-brothers or step-sisters.

If No, go to Q20 If Yes continue

19.1 How many? ☐☐ Number ❒ Don't know

☞ How many of your biological brothers or sisters have ever had self reported or doctor diagnosed:

19.2 Asthma? ☐☐ Number ❒ Don't know

19.3 COPD, COAD, chronic bronchitis, emphysema? ☐☐ Number ❒ Don't know

20. Do you, or did you, have any biological children? ❒ No ❒ Yes

If No, go to Q21 If Yes continue

20.1 How many? ☐☐ Number

20.2. How many of them have ever had self reported or doctor diagnosed asthma? ☐☐ Number ❒ Don't know

21. Has any member of your family or close relatives died from asthma? By family and close relatives I mean children, parents, siblings, nephews, nieces, grand parents, first cousins, uncles and aunts ❒ No ❒ Yes ❒ Don't know

If Yes: 21.1 How many? ☐☐ Number

22. Has any member of your family or close relatives died from COPD/COAD/Chronic Bronchitis/Emphysema? ❒ No ❒ Yes ❒ Don't know

If Yes: 22.1 How many? ☐☐ Number

When administering Q23 and Q25:

First ask the main question as given below i.e. "Have you used any inhaled medicines to help your breathing in the last 12 months?"

If the response is yes, get the participant to tell what medication/s he/she has used and find what group of drugs the participant's drug belongs to from the medication list provided with this questionnaire.

Then administer the sub questions under each medication (i.e. if a ***Short Acting beta-2-agonist inhaler is used complete 23.1 to 23.1.2.3)***

MEDICINES AND INHALERS

23. Have you used any inhaled medicines to help your breathing in the last 12 months? ❒ No ❒ Yes

If No, go to Q24 page 18. If Yes, continue

☞ **Which of the following have been used in the last 12 months?**

23.1 Short Acting beta-2-agonist inhalers? ❒ No ❒ Yes

If no go to Q 23.2. If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.1.1 In the last 12 months, have you used them for any of the following circumstances?

23.1.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.1.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.1.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.1.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.1.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.1.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.1.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.2 Long Acting beta-2-agonists? ❒ No ❒ Yes

If no go to Q 23.3. If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.2.1 In the last 12 months, have you used them for any of the following circumstances?

23.2.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.2.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.2.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.2.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.2.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.2.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.2.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.3 Anticholinergic Inhalers? ❒ No ❒ Yes

If no go to Q 23.4 If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.3.1 In the last 12 months, have you used them for any of the following circumstances?

23.3.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.3.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.3.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.3.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.3.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.3.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.3.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.4 Inhaled Steroids? ❒ No ❒ Yes

If no go to Q 23.5 If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.4.1 In the last 12 months, have you used them for any of the following circumstances?

23.4.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.4.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.4.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.4.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.4.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.4.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.4.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.5 Inhaled cromoglycate/nedocromil? ❒ No ❒ Yes

If no go to Q 23.6 If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.5.1 In the last 12 months, have you used them for any of the following circumstances?

23.5.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.5.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.5.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.5.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.5.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.5.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.5.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.6 Inhaled Compound Bronchodilators? ❒ No ❒ Yes

If no go to Q 23.7 If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.6.1 In the last 12 months, have you used them for any of the following circumstances?

23.6.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.6.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.6.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.6.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.6.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.6.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.6.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.7 Inhaled combination of steroids and long acting beta 2 agonist? ❒ No ❒ Yes

If no go to Q 23.8 If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.7.1 In the last 12 months, have you used them for any of the following circumstances?

23.7.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.7.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.7.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.7.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.7.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.7.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.7.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.8 Other inhaled medication? ❒ No ❒ Yes

If no go to Q 24 page 18. If Yes continue

Which one? _____

Which type of inhaler device do you use? _____

Strength/dose per puff (mcg)? _____

23.8.1 In the last 12 months, have you used them for any of the following circumstances?

23.8.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.8.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.8.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

23.8.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

23.8.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of puffs per month ☐☐

23.8.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of puffs per day during flare ups ☐☐

23.8.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of puffs per day ☐☐

24. Have you ever used inhaled steroids to help your breathing? ❒ No ❒ Yes

If No go to Q 25, if Yes continue

24.1 At what age did you start using inhaled steroids? ☐☐ years

24.2 In the past 5 years, how many months would you have used inhaled steroids on most days? ☐☐ months

25. Have you used any pills, capsules, tablets or medicines, other than inhaled medicines to help your breathing at any time in the last 12 months? ❒ No ❒ Yes

If No go to Q 26 page 22, if Yes continue

Which of the following have been used in the last 12 months?

25.1 Oral theophyllines ❒ No ❒ Yes

If no go to Q25.2 If Yes continue

Which one? _____

Strength/dose per tablet (mg)? _____

25.1.1 In the last 12 months, have you used them for any of the following circumstances?

25.1.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of tablets per month ☐☐

25.1.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of tablets per day during flare ups ☐☐

25.1.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of tablets per day ☐☐

25.1.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

25.1.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of tablets per month ☐☐

25.1.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of tablets per day during flare ups ☐☐

25.1.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of tablets per day ☐☐

25.2 Oral Steroids? ❒ No ❒ Yes

If no go to Q25.3 If Yes continue

Which one? _____

Strength/dose per tablet (mg)? _____

25.2.1 In the last 12 months, have you used them for any of the following circumstances?

25.2.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of tablets per month ☐☐

25.2.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of tablets per day during flare ups ☐☐

25.2.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of tablets per day ☐☐

25.2.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

25.2.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of tablets per month ☐☐

25.2.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of tablets per day during flare ups ☐☐

25.2.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of tablets per day ☐☐

25.3 Oral Anti-leukotrienes? ❒ No ❒ Yes

If no go to Q25.4 If Yes continue

Which one? _____

Strength/dose per tablet (mg)? _____

25.3.1 In the last 12 months, have you used them for any of the following circumstances?

25.3.1.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of tablets per month ☐☐

25.3.1.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of tablets per day during flare ups ☐☐

25.3.1.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of tablets per day ☐☐

25.3.2 Specifically, in the last 1 month, have you used them for any of the following circumstances?

25.3.2.1 For relief of symptoms and/or as needed to prevent predictable symptoms such as exercise induced asthma ❒ No ❒ Yes

If Yes: Average number of tablets per month ☐☐

25.3.2.2 For flare-ups or attacks ❒ No ❒ Yes

If Yes: Number of flare ups for which this medication was used in last 12 months ☐☐

Average number of days for which this medication was used at each flareup ☐☐

Average number of tablets per day during flare ups ☐☐

25.3.2.3 Regularly i.e daily (whether symptoms present or not) ❒ No ❒ Yes

If Yes: Average number of tablets per day ☐☐

25.4 Other Oral Medications? ❒ No ❒ Yes

25.4.1 List _____

_____

_____

26. Have you ever been prescribed home oxygen therapy? ❒ No ❒ Yes

If no go to Q27 If Yes continue

26.1 Are you currently using oxygen therapy at home? ❒ No ❒ Yes

26.2 For how many years have you been using oxygen therapy at home? ☐☐ years

26.3 How have you used oxygen therapy during the last month?

26.3.1 For relief of symptoms or when needed ❒ No ❒ Yes

26.3.2 For flare-ups or attacks ❒ No ❒ Yes

26.3.3 Regularly, on a daily basis ❒ No ❒ Yes

27. Have you ever had an influenza vaccination? ❒ No ❒ Yes

If yes 27.1 Have you been vaccinated for influenza in the last 12months? ❒ No ❒ Yes

28. Have you ever had a pneumonia vaccination? ❒ No ❒ Yes

If yes: 28.1 Have you been vaccinated for pneumonia in the last 5 years? ❒ No ❒ Yes

29. Have you ever been vaccinated or desensitised for allergy? ❒ No ❒ Yes

If yes: 29.1 Have you been vaccinated for allergy in the last 12 months? ❒ No ❒ Yes

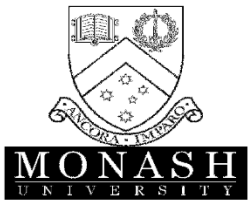
30. Have you had any other injections to help your breathing at any time in the last 12 months? ❒ No ❒ Yes

If yes: 30.1 What injections? _____

_____

Thank you for completing this questionnaire as part of the Tasmanian Asthma Study 36 year follow-up study.

Appendix 4- The TAHS 2005 laboratory follow-up clinical testing







TASMANIAN HEALTH STUDY: LABORATORY PHASE

LAB BOOKLET

TASMANIAN TESTING CENTRES

Research Investigators:

- Dr Shyamali Dharmage, The University of Melbourne
- Professor E. Haydn Walters, University of Tasmania
- Professor Michael Abramson, Monash University
- Associate Professor David Johns, The University of Tasmania
- Professor John Hopper, The University of Melbourne
- Dr Mark Jenkins, The University of Melbourne
- Dr Geza Benke, Monash University

Participant ID: | | | | |

Participant initials: | | | |

Participant DOB: | | | | (day / month / year)

Appointment date: | | | | (day / month / year)

Centre number: | |

Scientist initials: | | |

Sample number: 2

(Centre number: Royal Hobart Hospital= 1, Northern Lung Function Service= 2, Burnie Physiology= 3, Alfred Hospital= 4)

PARTICIPANT CONTACT DETAILS

Participant ID: | | | | |

Please record your full name and contact details below:

Full name: _____

Street address: _____

Suburb: _____ State: _____ Postcode: _____

Home phone: _____

Work phone: _____

Mobile phone: _____

Email address: _____

A lot of money and staff time goes into just trying to locate participants for follow-up research studies. It would be appreciated if you could provide the name and contact details of one person who is not part of your immediate family and who will know your whereabouts in future years (and lives at a different address to you). We would only contact this person if another follow-up study is done in future and we can't locate you through other means. These details will be kept confidential.

Person's name: _____

Relationship: _____

Street address: _____

Suburb: _____ State: _____ Postcode: _____

Home phone: _____

Work phone: _____

Mobile phone:

FAMILY CONTACT DETAILS

You are probably aware that in 1968 a short health survey was also done on your parents and brothers and sisters. We hope to receive funding in the future to do a follow-up postal survey on the health of these family members.

	Yes	*No*
Can we contact you in future so that we can update your family's contact details?	☐	☐

We would use these details to send them a voluntary health survey. Providing your family's contact details does not commit them to take part in the survey- they can still choose whether they want to participate or not.

PARTICIPANT CONSENT FORM

Participant ID: | | | | |

Thank you for participating in this medical research project. Signing this form simply means that you have agreed to take part in all or some of the laboratory phase of the Tasmanian Health Study. It does not remove any of your rights as a research participant.

The testing will take about one and a half hours of your time and it involves:

1. completing a questionnaire about your respiratory health
2. provide information about your employment and residence history so we can examine your exposure to dust and fumes.
3. having a skin prick test to determine if you have any sensitivity to some common allergens
4. participating in 3 breathing tests (spirometry, a lung volume test and a gas transfer test); and
5. giving a blood sample of 30mls.

If you have any questions or concerns about these tests please discuss them with the scientist.

A report of the main results will be posted to all lab participants at the end of the study.

Scientist comments: _____

_____

_____

I have been informed that the general purpose of this medical research is to identify the risks for respiratory health problems in adults. The tests and any foreseeable effects of my participation have been explained to me.

I understand that my involvement in this research is voluntary and that I am free to withdraw at anytime without giving a reason. I know that I can also withdraw any information that I have previously supplied. I understand that by law my personal information and the results of my tests must be stored securely for at least 5 years and will be kept confidential within the limits of the law. My identity will not be revealed in the results as only group information will be used in publications.

I am aware that there is no direct benefit to me from being involved in this research except for the provision of information about sensitivity that I might have to the allergens and comment about the results of my breathing tests. I understand that with my consent this information can be sent to my own doctor. Information sent to my doctor will not be taken to provide a specific diagnosis of any condition or illness.

I agree to participate in all or part of this research testing.

Participant's name (printed): _____

Participant's signature: _____ Date: _____

Depending on the results of this research, we may wish to test the sensitivity of airways in some participants. Would you be willing to do another short breathing test in 2 to 3 years time, if you are selected?	*Yes*	*No*
	☐	☐

CONSENT TO PROVIDE TEST RESULTS TO YOUR DOCTOR

This section is only to be completed if the participant's results are to be sent to their doctor.

Participant ID: | | | | |

If the scientist feels it would be beneficial for you and if you agree by signing below, we can send your test results to your doctor. This may be recommended if you are found to have allergies or if your breathing tests are substantially below the predicted values.

We can also send your test results to your doctor to be added to your medical file at your request.

Signing below means you are providing consent for us to release your test result information to your doctor.

Participant name (printed): _____

Participant's signature: _____ Date: _____

Please provide your doctor's details below:

Your doctor's name: _____

The clinic name: _____

The clinic address: _____

_____

Doctor's phone number: _____

SKIN PRICK TEST FORM

Participant ID: | | | | |

-ve control	*Dustmite*	**NEGATIVE CONTROL** 1st diam 2nd diam	**D.PTERONYSSINUS** 1st diam 2nd diam
Cat	*Hormodendrum*	**CAT** 1st diam 2nd diam	**HORMODENDRUM** 1st diam 2nd diam
Alternaria	*Penicillium*	**ALTERNARIA** 1st diam 2nd diam	**PENICILLIUM** 1st diam 2nd diam
Aspergillus	*Rye grass*	**ASPERGILLUS** 1st diam 2nd diam	**RYE GRASS** 1st diam 2nd diam
Mixed grasses	*+ve control*	**MIXED GRASSES** 1st diam 2nd diam	**POSITIVE CONTROL** 1st diam 2nd diam

LUNG FUNCTION QUESTIONNAIRE

Participant ID: ☐☐☐☐

1. Participant's height ☐☐☐ cm

2. Participant's weight ☐☐☐.☐ kg

3. Have you used a puffer or inhaler in the last 24 hours? ☐ No ☐ Yes
   If yes: 3.1 What inhaler(s) did you use and how many hours ago was the last dose taken?
   _____ ☐☐ Hours
   _____ ☐☐ Hours

4. Have you taken any medication for breathing (other than inhalers) in the last 24 hours? ☐ No ☐ Yes
   If yes: 4.1 Which medication(s) did you take and how many hours ago was the last dose taken?
   _____ ☐☐ Hours
   _____ ☐☐ Hours

5. Have you had a cigarette (or any other tobacco product) in the last 24 hours? ☐ No ☐ Yes
   If yes: 5.1 How many hours ago was your last smoke? ☐☐ Hours

6. Have you taken an antihistamine (a medication for allergy including hay fever) or cough medicine in the last 72 hours? ☐ No ☐ Yes
   If yes: 6.1 What medicine(s) did you use and how many hours ago was the last dose taken?
   _____ ☐☐ Hours
   _____ ☐☐ Hours

7. Have you taken any medication for high blood pressure or a heart condition, or used eye drops to treat glaucoma in the last 72 hours? ☐ No ☐ Yes
   If yes: 7.1 Which medication(s) did you take and how many hours ago was the last dose taken?
   _____ ☐☐ Hours
   _____ ☐☐ Hours

8. Have you had a respiratory infection in the last 3 weeks? ☐ No ☐ Yes
   If yes: 8.1 How many days ago did it end? ☐☐ Days

9. How many hours ago did you have your last meal? ☐☐ Hours

10. If female: what was the date of your last menstrual period (first day of period)? / /
    Tick if pregnant ☐ *or have no periods* ☐

11. SPIROMETRY	Pre-BD	Post-BD
FEV_1 (litres)	☐☐.☐☐	☐☐.☐☐
FVC (litres)	☐☐.☐☐	☐☐.☐☐
FEV_1/FVC (%)	☐☐.☐☐	☐☐.☐☐
$FEF_{25-75\%}$ (litres/second)	☐☐.☐☐	☐☐.☐☐
PEF (litres/second)	☐☐.☐☐	☐☐.☐☐
$FEF_{50\%}$ (litres/second)	☐☐.☐☐	☐☐.☐☐
$FIF_{50\%}$ (litres/second)	☐☐.☐☐	☐☐.☐☐
Shape of flow volume loop pre-BD only (to be assessed by DJ): _____		

12. SINGLE BREATH TLco (post-BD)	Post-BD
TLco (ml/min/mmHg) (uncorrected)	☐☐.☐☐
VA (litres)	☐.☐☐
TLco/VA (ml/min/mmHg/litre)	☐.☐☐
Inspiratory VC (litres)	☐.☐☐

13. LUNG VOLUMES AND CAPACITIES (post-BD)	Post-BD
TLC (litres)	☐☐.☐☐
FRC (litres)	☐☐.☐☐
RV (litres)	☐.☐☐
VC (litres)	☐.☐☐
IC (litres)	☐.☐☐
RV/TLC (%)	☐☐.☐☐

14. 29ML OF BLOOD TO BE COLLECTED
1st tube- ACD tube (yellow top), 2nd tube- Serum tube (red top), 3rd tube- EDTA tube (purple top)

15. HB AND COHB	Post-BD
Hb g/dl	☐☐.☐
COHb % (or ppm for expired CO)	☐☐☐.☐

Additional comments: _____

CHECK LIST

Participant ID: | | | | |

	Yes	No	Comments:
1. Has the work history calendar & residence history form been collected & checked?	☐	☐	
2. Has the family contact details form been checked for completeness and collected?	☐	☐	
3. Has the participant read the plain language statement and had the opportunity to discuss any concerns?	☐	☐	
4. Has the participant signed the consent form?	☐	☐	
5. Has the skin prick test been performed?	☐	☐	
6. Have the lung function tests been carried out?			
Pre- bronchodilator spirometry?	☐	☐	
Post- bronchodilator spirometry?	☐	☐	
TLco test (post BD)?	☐	☐	
Lung volumes and capacities test (post BD)?	☐	☐	
Is the lung function questionnaire complete?	☐	☐	
Have the lung function results been printed and attached to the lab booklet?	☐	☐	
7. Has the 29 ml blood sample been collected?			
1st tube- ACD tube- yellow top (9ml)?	☐	☐	
2nd tube- Serum tube- red top (10ml)?	☐	☐	
3rd tube- EDTA tube- purple top (10ml)?	☐	☐	
Date and time blood collected from participant: / /			am pm
8. Has the haemoglobin been measured and recorded on page 8?	☐	☐	
9. Has carboxyhaemoglobin been measured and recorded on page 8?	☐	☐	
10. Has Hb and CoHb been measured using venous blood or from a finger prick?	☐ Venous	☐ Finger	

Appendix 5- The TAHS 2002-2008 follow-up lifetime work history calendar

WORK HISTORY CALENDAR & RESIDENCE HISTORY FORM

Tasmanian Health Study

Participant name: _____ **ID number:** _____ **Appt Date:** _____

Thank you for volunteering for this study. To ensure that your lab visit is as quick as possible it would be appreciated if you could take a few mintues to complete the "Work History Calendar" and "Residence History Form", which are on the centre and back pages. The instructions for each form are below.

All information you provide for this research will be kept strictly confidential and only group data will be used in reports so no individuals can be identified.

If you have booked a lab appointment please bring this form with you and give it to the scientist. Otherwise please post it in the envelope provided.

If you have any problems or questions about either of these two forms please call us.

Tasmanian participants can call **Dr Desiree Mesaros** on **1800 207 765**

Victorian participants can call **Billy Skoric** on **(03) 9276 3476**

WORK HISTORY CALENDAR INSTRUCTIONS (centre page)

The information you provide in the work history calendar will help to determine if work place exposures to dust and fumes contribute to respiratory illness.

To fill in the calendar you will need to think about jobs you have done over your lifetime. Please list the jobs you have held over your working life starting with your most recent or current position.

For each job you have had, please list the job title, the type of industry in which you were employed, and the name of your employer. Please also record the number of days per week usually worked for each job. If a job did not follow a weekly cycle then please explain by writing a brief explanation, such as "four days on and four days off" for example. Please also record the number of hours per day that you were usually at work.

WORK HISTORY CALENDAR

Please start with your current or most recent job and fill in as many jobs as you can over your entire working life. Thank you!

	Job title (e.g.: teacher, nurse, secretary, manager, student, accountant, clerk, engineer, waitress)	**Industry** (e.g.: education, retail, health, mining, food, hospitality, transport manufacturing, public service, insurance, banking, advertising)	**Name of employer**	**Number of days per week**	**Hours per day**	**Year job started**	**Year job ended**
1							
2							
3							
4							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							

PTO →

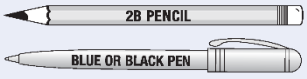
Appendix 6- The TAHS 2010 follow-up postal survey questionnaire

TAHS
Tasmanian Longitudinal Health Study

Parents Follow-up Study

Thank you for your help with this medical research.
All information you provide is kept strictly confidential.
If you have any questions please call 1800 110 711 (free call in Australia)

INSTRUCTIONS



- Please use a blue or black ballpoint pen or a 2B pencil
- DO NOT USE red or felt-tip pens
- Erase mistakes fully
- Make no stray marks

PLEASE MARK LIKE THIS:
NOT LIKE THIS:

Your date of birth:

ID Number:

Family ID:

Current contact details:

Current name:

Current address:

Please provide your phone numbers:

Home:

Work:

Mobile:

Today's date:

GENERAL DEMOGRAPHIC INFORMATION

1. What is your height without shoes? (Answer either in feet & inches OR centimeters.)

☐☐ feet and ☐☐ inches **OR** ☐☐☐ centimeters

2. What is your weight? (Answer either in stone & pounds OR in kilograms.)

☐☐ stone and ☐☐ pounds **OR** ☐☐☐ kilograms

3. What is the highest educational or vocational qualification that you have completed? (mark one only)

- ○ Grade 1 to 6
- ○ Grade 7 to 9
- ○ Grade 10 or 11
- ○ Grade 12 or equivalent (eg. Higher School Certificate)
- ○ Trade/ Apprenticeship (eg. Hairdresser, electrician, plumber)
- ○ Certificate or Diploma (eg. Child care, technician etc)
- ○ University degree (eg. Bachelor)
- ○ Higher University degree (eg. Graduate diploma, masters, PhD)

4. Are you currently employed (including self-employed)? (mark one only)

○ Yes ○ No ○ No, studying ○ No, retired

5. What is/was your main occupation? (mark one only)

- ○ Manager or administrator (eg. Magistrate, general manager, school principal, director of nursing)
- ○ Professional (eg. Scientist, nurse, allied health professional, teacher, artist)
- ○ Associate professional (eg. Technician, manager, police officer, small business owner)
- ○ Tradesperson or related worker (eg. Hairdresser, gardener, florist)
- ○ Advanced clerical or service worker (eg. Secretary, flight attendant, law clerk, personal assistant)
- ○ Intermediate clerical/sales/service worker (eg. Administration worker, child care or hospitality worker)
- ○ Intermediate production or transport worker (eg. Machine operator, bus driver, sewing machinist)
- ○ Elementary clerical/sales/service worker (eg. Filing/mail clerk, parking inspector, sales assistant)
- ○ Labourer or related worker (eg. Cleaner, factory worker, farm hand, kitchen hand)
- ○ House person

6. What is your marital status? (mark one only)

- ○ Never married
- ○ Widowed
- ○ Divorced
- ○ Separated but not divorced
- ○ De facto
- ○ Married

GENERAL HEALTH

7. Have you ever been allergic to any of the following? (tick all that apply)

- ○ Foods
- ○ Medicine
- ○ Dust
- ○ Animals
- ○ Pollen, grass, trees or flowers
- ○ None of the above

8. Have you ever had hayfever or nasal allergies (that is sneezing, running or blocked nose when you do not have a cold or flu)?

○ Yes → **CONTINUE** ○ No → **GO TO Q9**

8.1 Have you had this problem in the last 12 months? ○ No ○ Yes

8.2 Was this problem accompanied by itchy or watery eyes? ○ No ○ Yes

8.3 How old were you when you first had hayfever or nasal allergies? ☐☐ (age in years)

9. When you are near animals, such as cats, dogs, or horses; near feathers, including pillows, quilts or doonas; or in a dusty part of the house, do you ever: (mark all that apply)

○ Start to cough?
○ Start to wheeze?
○ Get a feeling of tightness in the chest?
○ None of the above
○ Start to feel short of breath?
○ Get a runny or stuffy nose or start to sneeze?
○ Get itchy or watery eyes?

10. When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ever: (mark all that apply)

○ Start to cough?
○ Start to wheeze?
○ Get a feeling of tightness in the chest?
○ None of the above
○ Start to feel short of breath?
○ Get a runny or stuffy nose or start to sneeze?
○ Get itchy or watery eyes?

→ **CONTINUE TO Q10.1**

10.1 If yes, which time of the year does this happen? (mark all that apply)

○ Winter ○ Spring ○ Summer ○ Autumn

11. Have you ever had eczema or any kind of skin allergy? ○ No ○ Yes

12. Have you ever had an itchy rash that was coming and going for at least 6 months?

○ Yes → **CONTINUE** ○ No → **GO TO Q13**

12.1 How old were you when you first had this itchy rash? ☐☐ (age in years)

12.2 Have you had this itchy rash in the last 12 months? ○ No ○ Yes

12.3 Has this rash at any time affected any of the following places: (mark all that apply)

○ Fold of the elbows ○ In front of the ankles ○ Around the neck, ears or eyes
○ Behind the knees ○ Under the buttocks ○ None of the above

13. Have you ever had any food allergies?

○ Yes → **CONTINUE** ○ No → **GO TO Q14**

13.1 To what food are you allergic? (mark all that apply)

○ Peanut ○ Soy ○ Sesame ○ Fish
○ Egg ○ Milk ○ Wheat ○ Other (please specify) ☐

13.2 Who diagnosed these food allergies? (mark one)

○ Doctor
○ Self-diagnosis
○ Other health professional

13.3 Have you ever had a skin prick test (SPT) to confirm this food allergy? ○ No ○ Yes

13.4 Have you ever had a food challenge at an allergy clinic to confirm this food allergy? ○ No ○ Yes

RESPIRATORY SYMPTOMS

14. Are you troubled by shortness of breath?

○ Yes → **CONTINUE** ○ No → **GO TO Q15**

14.1 Do you get shortness of breath only with strenuous exercise? ○ No ○ Yes

14.2 Do you get short of breath when hurrying on level ground or walking up a slight hill? ○ No ○ Yes

14.3 Do you have to walk slower than other people of your age because of breathlessness? ○ No ○ Yes

14.4 Do you have to stop for breath when walking at your own pace on level ground? ○ No ○ Yes

14.5 Do you ever get short of breath when resting? ○ No ○ Yes

15. Have you had wheezing or whistling in your chest in the last 12 months? (Wheezing means a whistling sound, however high or low pitched and however faint).

○ Yes → **CONTINUE** ○ No → **GO TO Q16**

15.1 Have you been at all breathless when the wheezing noise was present? ○ No ○ Yes

15.2 Have you had this wheezing or whistling when you did not have a cold? ○ No ○ Yes

16. Have you, at any time in the last 12 months, woken up with a feeling of tightness in your chest?

○ No ○ Yes

17. Have you, at any time in the last 12 months, been woken at night by an attack of shortness of breath?

○ No ○ Yes

18. Have you, at any time in the last 12 months, had an attack of shortness of breath at rest?

○ No ○ Yes

19. Have you, at any time in the last 12 months, had an attack of shortness of breath after exercise?

○ No ○ Yes

SNORING

20. During the last month, do you or have you been told you snore loudly in sleep?

○ Yes → **CONTINUE** ○ No → **GO TO Q21** ○ Don't know → **GO TO Q21**

20.1 On average, how often do you snore loudly in sleep?
○ Rarely, less than once a week ○ 5–7 times per week
○ 1–2 times per week ○ Don't know
○ 3–4 times per week

21. During the last month, do you or have you been told you snort or gasp in sleep?

○ Yes → **CONTINUE** ○ No → **GO TO Q22** ○ Don't know → **GO TO Q22**

21.1 On average, how often do you snort or gasp in sleep?
○ Rarely, less than once a week ○ 5–7 times per week
○ 1–2 times per week ○ Don't know
○ 3–4 times per week

22. During the last month, do you or have you been told you choke or stop breathing in sleep?

○ Yes → **CONTINUE** ○ No → **GO TO Q23** ○ Don't know → **GO TO Q23**

22.1 On average, how often do you choke or stop breathing in sleep?
○ Rarely, less than once a week ○ 1–2 times per week ○ 3–4 times per week ○ 5–7 times per week ○ Don't know

23. During the last month, have you had excessive sleepiness during the day? ○ No ○ Yes

COUGH & PHLEGM

24. Do you usually cough when you do not have a cold?

○ Yes → **CONTINUE** ○ No → **GO TO Q25**

24.1 Are there months in which you cough on most days?

○ Yes → **CONTINUE** ○ No → **GO TO Q25**

24.1.1 Do you cough on most days for at least three months of each year? ○ No ○ Yes

24.1.2 For how many years have you had this cough?

○ Less than 2 years ○ 2 -5 years ○ More than 5 years

25. Do you usually have phlegm in your chest when you do not have a cold?

○ Yes → **CONTINUE** ○ No → **GO TO Q26**

25.1 Are there months in which you have phlegm in your chest on most days?

○ Yes → **CONTINUE** ○ No → **GO TO Q26**

25.1.1 Do you bring up this phlegm on most days for at least three months of each year? ○ No ○ Yes

25.1.2 How many years have you had this phlegm?

○ Less than 2 years ○ 2 -5 years ○ More than 5 years

26. Have you, at any time in your life, suffered from cough with phlegm in the chest (with or without a cold)?

○ Yes → **CONTINUE** ○ No → **GO TO Q27**

26.1 Have you had cough with phlegm on most days for at least three months and for two years in a row? ○ No ○ Yes

RESPIRATORY CONDITIONS

27. Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing? (Regard asthma and wheezy breathing as being much the same for this question.)

○ Yes → **CONTINUE** ○ No → **GO TO Q28**

27.1 How old were you when you had your first attack of asthma or wheezy breathing? ☐☐ (age in years)

27.2 How old were you when you had your most recent attack of asthma or wheezy breathing? ☐☐ (age in years)

27.3 Have you had an attack of asthma or wheezy breathing in the last 12 months? ○ No ○ Yes

27.4 Have you taken any medicines including inhalers or tablets for asthma or wheezy breathing, in the last 12 months? ○ No ○ Yes

28. Has a doctor ever said that you have or have had asthma?

○ Yes → **CONTINUE** ○ No → **GO TO Q29**

28.1 How old were you when you were told you had this condition? ☐☐ (age in years)

28.2 Have you taken any medicine (including inhalers or tablets) for this condition in the last three months? ○ No ○ Yes

29. Has a doctor ever said that you have or have had chronic bronchitis?

○ Yes → **CONTINUE** ○ No → **GO TO Q30**

29.1 How old were you when you were told you had this condition? ☐☐ (age in years)

29.2 Have you taken any medicine (including inhalers or tablets) for this condition in the last three months? ○ No ○ Yes

30. Has a doctor ever said that you have or have had emphysema?

○ Yes → **CONTINUE** ○ No → **GO TO Q31**

30.1 How old were you when you were told you had this condition? ☐☐ (age in years)

30.2 Have you taken any medicine (including inhalers or tablets) for this condition in the last three months? ○ No ○ Yes

31. Has a doctor ever said that you have or have had chronic obstructive pulmonary disease (COPD) or chronic obstructive airways disease?

○ Yes → **CONTINUE** ○ No → **GO TO Q32**

31.1 How old were you when you were told you had this condition? ☐☐ (age in years)

31.2 Have you taken any medicine (including inhalers or tablets) for this condition in the last three months? ○ No ○ Yes

32. Has your doctor ever told you that you have or had obstructive sleep apnoea?

○ Yes → **CONTINUE** ○ No → **GO TO Q33**

32.1 How old were you when you were told you had this condition? ☐☐ (age in years)

32.2 Are you currently being treated for obstructive sleep apnoea with CPAP, surgery, adequate weight loss or other device? ○ No ○ Yes

CHEST COLDS & CHEST ILLNESSES

33. If you get a cold, does it usually go to your chest? (Usually means more than half of the time)

○ No ○ Yes ○ Don't know

34. During the past 3 years, have you had any chest illnesses that have kept you off work, indoors at home, or in bed?

○ Yes → **CONTINUE** ○ No → **GO TO Q35**

34.1 Did you produce phlegm with any of the chest illnesses? ○ No ○ Yes

34.2 In the last 3 years, how many such illnesses, with increased phlegm, did you have which lasted a week or more? (if none enter zero) ☐☐ Number of illnesses

35. Have you ever had Pneumonia? ○ Yes → **CONTINUE** ○ No → **GO TO Q36**

35.1 Was this confirmed by a doctor? ○ No ○ Yes

35.2 At what age did you first have it? ☐☐ (age in years)

35.3 How many times have you had it? ☐☐ (number of times)

35.4 Have you ever been hospitalised for Pneumonia? ○ No ○ Yes

36. Have you ever been hospitalised for any other chest illness?

○ Yes → **CONTINUE** ○ No → **GO TO Q37**

Diagnosis	*Age at first occurrence*	*Number of occurrences*

MEDICAL CONDITIONS

37. Has a doctor ever told you that you have/had any of the following conditions? (mark all that apply)

- ○ Angina, heart attack or myocardial infarction
- ○ Transient ischaemic attack (TIA) or a stroke
- ○ High blood pressure or Hypertension
- ○ High levels of cholesterol/high triglycerides
- ○ Diabetes or high sugar levels in the blood or urine
- ○ Cancer
- ○ Rheumatoid arthritis
- ○ Psychiatric/mental health problem
- ○ Multiple Sclerosis
- ○ Thyroid problems
- ○ Lupus/Systemic Lupus Erythematosus

SMOKING

38. In your lifetime, have you smoked at least 100 cigarettes or equal amount of cigars, pipes, or any other tobacco product?

○ Yes → **CONTINUE** ○ No → **GO TO Q39**

38.1 How old were you when you started smoking? ☐☐ (age in years)

38.2 Do you currently smoke (within the last 4 weeks)?

- ○ Yes, daily → **CONTINUE**
- ○ Yes, less than weekly → **CONTINUE**
- ○ Yes, at least weekly → **CONTINUE**
- ○ Not at all → **GO TO Q38.2.2**

38.2.1 On average, how much do you smoke (total number of cigarettes or equivalent product)? (Provide the average number per day OR per week OR per month.)

☐☐ per day → **GO TO Q39** **OR** ☐☐ per week → **GO TO Q39** **OR** ☐☐ per month → **GO TO Q39**

38.2.2 How old were you when you last stopped smoking? ☐☐ (age in years)

38.2.3 On average, during periods when you smoked, how much did you smoke (total number of cigarettes or equivalent product)? (Provide the average number per day OR per week OR per month.)

☐☐ per day **OR** ☐☐ per week **OR** ☐☐ per month

39. Not counting yourself, how many people in your household currently smoke regularly (most days of the week) inside the house? (If none, enter zero) ☐☐ Number of people

40. On average, how many hours per day are you exposed to other people's tobacco smoke (work and/or home)? ☐☐ Number of hours

CHILDHOOD ENVIRONMENT

41. What term best describes the place you lived most of the time when you were under the age of five years? (mark one box only)

○ Farm ○ Country town ○ Suburb of a city ○ Inner city ○ Don't know

42. How many of your brothers, sisters or other children regularly slept in your bedroom before you were five years old, not including yourself? ☐☐ Number of children

43. Did you have a serious respiratory infection before the age of five years?

○ No ○ Yes ○ Don't know

44. Did you go to school, pre-school, kindergarten, or a day care centre before the age of five years?

○ Yes → **CONTINUE** ○ No → **GO TO Q45** ○ Don't know → **GO TO Q45**

44.1 At what age did you first attend a school, pre-school, kindergarten, or day care? ☐☐ age in years

45. Did your father smoke...

45.1 When you were less than 5 years? ○ No ○ Yes ○ Don't know

45.2 When you were aged 5-15 years? ○ No ○ Yes ○ Don't know

46. Did your mother smoke...

46.1 When you were less than 5 years? ○ No ○ Yes ○ Don't know

46.2 When you were aged 5-15 years? ○ No ○ Yes ○ Don't know

47. Was there a cat in your home...

47.1 When you were less than 5 years? ○ No ○ Yes ○ Don't know

47.2 When you were aged 5-15 years? ○ No ○ Yes ○ Don't know

48. Did you have carpet (or a rug) covering the floor in your bedroom...

48.1 When you were less than 5 years? ○ No ○ Yes ○ Don't know

48.2 When you were aged 5-15 years? ○ No ○ Yes ○ Don't know

49. What was the main type of heating your home had when you were under the age of five years? (mark one only)

○ Gas ducted central heating
○ Coal or wood fire
○ Gas room heater
○ Electric heater (eg. Radiator, fan or dimplex-type)
○ Other central heating (eg. Electric, hydronic, slab floor)
○ Reverse cycle air-conditioning
○ Other
○ No heating

If you are female, please continue. If you are male, thank you for your time and contribution to the TAHS

SUPPLEMENT FOR WOMEN

50. Have you ever had a menstrual period?

○ Yes → **CONTINUE** ○ No → **GO TO Q51**

50.1 What was your age when you had your first period? ☐☐ (age in years)

50.2 Have you had a menstrual period in the last 12 months?

○ No → **GO TO Q50.3** ○ Yes → **GO TO Q51** ○ Don't know → **GO TO Q51**

50.3 Have your menstrual periods stopped permanently or only temporarily due to pregnancy, breast feeding or other condition?

○ Stopped permanently → **CONTINUE** ○ Stopped temporarily → **GO TO Q51**

50.4 How old were you when your periods stopped permanently? ☐☐ (age in years)

51. Have you ever used birth control pills or other hormonal contraceptives (implants or injections)?

○ Yes → **CONTINUE** ○ No → **GO TO Q52**

51.1 At what age did you first use birth control pills or other hormonal contraceptives? ☐☐ (age in years)

51.2 Over your whole lifetime, in total how many months or years have you taken birth control pills or other hormonal contraceptives?

☐☐ months **OR** ☐☐ years

52. Have you ever been pregnant in the past?

○ Yes → **CONTINUE** ○ No → **GO TO Q55**

53. How many live births have you had? ☐☐ (if none, please enter '0')

54. How many miscarriages, abortions or stillbirths have you had? ☐☐ (if none, please enter '0')

55. Have you ever had a mammogram? ○ No ○ Yes

56. Have you ever taken oestrogen, progesterone or other female hormones for menopause (that is, prescription hormone replacement therapy or HRT)? The preparation may be pills, injections or skin patches. This question does not include birth control pill or hormonal contraceptives.

○ No ○ Yes

For each of your children, please answer the following questions about your pregnancy and their early life. If more than 8 children, please record the details on a separate piece of paper.

Child's name and date of birth:			
57. What was your age when you became pregnant? (age in years)	☐☐	☐☐	☐☐
58. What city did you spend the majority of your pregnancy with this child?			
59. Were you working indoors during your pregnancy with this child?	○ No ○ Full time ○ Part time ○ Casual	○ No ○ Full time ○ Part time ○ Casual	○ No ○ Full time ○ Part time ○ Casual
60. What was this child's birth weight?			
61. How long were you pregnant before delivery of this child (in weeks)?	☐☐	☐☐	☐☐
62. Did you get this birth information from the child's maternal & child health booklet?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
63. What term best describes the place you lived most of the time when this child was under the age of five years?	○ Farm ○ Rural town ○ Suburbs ○ Inner city	○ Farm ○ Rural town ○ Suburbs ○ Inner city	○ Farm ○ Rural town ○ Suburbs ○ Inner city
64. Did this child sleep in a bedroom with his/her brothers and sisters before the age of five years?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
65. Did this child have a serious respiratory infection before the age of five years?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
66. Did this child go to school, pre-school, kindergarten, or a day care centre before the age of five years?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
67. Did the child's father smoke during your pregnancy with this child?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
68. Did you smoke during your pregnancy with this child?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
69. Did you keep cats in your home before this child was 5 years old?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
70. Was this child exposed to swimming pools in the first 2 years of life?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
71. Was this child bathed with soap in the first 1 year of life?	○ Always ○ Sometimes ○ Never	○ Always ○ Sometimes ○ Never	○ Always ○ Sometimes ○ Never
72. Has this child at any time before the age of 7 years, suffered from attacks of asthma or wheezy breathing?	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No

☐☐	☐☐	☐☐	☐☐	☐☐
○ No ○ Full time ○ Part time ○ Casual	○ No ○ Full time ○ Part time ○ Casual	○ No ○ Full time ○ Part time ○ Casual	○ No ○ Full time ○ Part time ○ Casual	○ No ○ Full time ○ Part time ○ Casual
☐☐	☐☐	☐☐	☐☐	☐☐
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Farm ○ Rural town ○ Suburbs ○ Inner city	○ Farm ○ Rural town ○ Suburbs ○ Inner city	○ Farm ○ Rural town ○ Suburbs ○ Inner city	○ Farm ○ Rural town ○ Suburbs ○ Inner city	○ Farm ○ Rural town ○ Suburbs ○ Inner city
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No
○ Always ○ Sometimes ○ Never	○ Always ○ Sometimes ○ Never	○ Always ○ Sometimes ○ Never	○ Always ○ Sometimes ○ Never	○ Always ○ Sometimes ○ Never
○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No	○ Yes ○ No

Appendix 7- The TAHS 2010 follow-up laboratory questionnaire



The Tasmanian Longitudinal Health Study

What are the causes of increased airway sensitivity in middle-age?

Thank you for your help with this medical research.
All information you provide is kept strictly confidential.
If you have any questions please call **1800 110 711** (free call in Australia)

Current Contact Details:

Current name:	
DOB:	
IDnumber:	FamilyID:
Current address:	

Please provide your phone numbers:

Home: ( )

Work: ( )

Mobile:

Today's date:

For questions where the subject has to choose one answer, read out the question and all the categories before expecting them to respond. Definitions of ambiguous terms are given in text boxes. To standardise the questionnaire administration across centres, avoid providing any further explanation other than what is given in the questionnaire

GENERAL DEMOGRAPHIC INFORMATION

A. What is your height without shoes?
(Answer either in feet & inches **OR** centimeters.)

☐☐ *feet and* ☐ *inches*

OR

☐☐☐ *Centimeters*

B. What is your weight?
(Answer either in stone & pounds **OR** in kilograms.)

☐☐ *stone and* ☐☐ *pounds*

OR

☐☐☐ *kilograms*

C. What is the highest educational or vocational qualification that you have completed? ***(tick one only)***

- ☐ Grade 1 to 6
- ☐ Grade 7 to 9
- ☐ Grade 10 or 11
- ☐ Grade 12 or equivalent (eg. Higher School Certificate)
- ☐ Trade/ Apprenticeship (eg. Hairdresser, electrician, plumber)
- ☐ Certificate or Diploma (eg. Child care, technician etc)
- ☐ University degree (eg. Bachelor)
- ☐ Higher University degree (eg. Graduate diploma, masters, PhD)

D. Are you **currently employed** (including self-employed)?
(tick one only)

- ☐ Yes
- ☐ No
- ☐ No, studying
- ☐ No, retired

E. What is/was your **main occupation**? ***(tick one only)***

Manager or administrator ..... ☐
(eg. Magistrate, general manager, school principal, director of nursing)

Professional ..... ☐
(eg. Scientist, nurse, allied health professional, teacher, artist)

Associate professional ..... ☐
(eg. Technician, manager, police officer, small business owner)

Tradesperson or related worker ..... ☐
(eg. Hairdresser, gardener, florist)

Advanced clerical or service worker ..... ☐
(eg. Secretary, flight attendant, law clerk, personal assistant)

Intermediate clerical, sales, service worker ..... ☐
(eg. Administration worker, child care worker, nursing assistant, hospitality worker)

Intermediate production or transport worker ..... ☐
(eg. Machine operator, bus driver, sewing machinist)

Elementary clerical, sales or service worker ..... ☐
(eg. Filing/mail clerk, parking inspector, sales assistant, housekeeper)

Labourer or related worker ..... ☐
(eg. Cleaner, factory worker, farm hand, kitchen hand)

House person..... ☐

F. What is your martial status? *(tick one only)*

☐ Never married = 1
☐ Widowed = 2
☐ Divorced = 3
☐ Separated but not divorced = 4
☐ De facto = 5
☐ Married = 6

HOME ENVIRONMENT

First I am going to ask few questions about your home and the area where you live.

1a. What is <u>your current postcode</u>? ☐☐☐☐

1. Have you changed residence from when we last interviewed you (interviews were between 2004 and 2008)? ❒ No ❒ Yes

If no, go to Q2

If Yes☞ **1.1** For how many years have you lived in your present home?
(<1year code as 1) ☐☐

1.2 In which decade was your present home built? *Tick one* ☑

- ❒ Before 1940
- ❒ 1941-1960
- ❒ 1961-1970
- ❒ 1971-1980
- ❒ 1981-1990
- ❒ 1990- Present
- ❒ Don't know

1.3 What is the base structure of your home? *Tick one* ☑

- ❒ Concrete slab
- ❒ Stumps and wooden flooring
- ❒ Combination of above
- ❒ Don't know

2. How old is the mattress in your bed? *Tick one* ☑

- ❒ Less than 12 months old
- ❒ 1-5 years old
- ❒ More than 5 years old
- ❒ Don't know
- ❒ Not relevant (e.g. waterbed)

3. Is there fitted carpet in the bedroom? ❒ No ❒ Yes

If Yes☞ 3.1 What is the age of the carpet? *Tick one*

- ❒ Less than 12 months old
- ❒ 1 - 5 years old
- ❒ More than 5 years old
- ❒ Don't know

4. On average, how often is your bedroom vacuumed, or if it has a hard floor, how often is it swept or mopped? (*Tick one)*

- ❒ 5 or more times each week
- ❒ 2-4 times each week
- ❒ Once a week
- ❒ Less than once a week but more than once a month
- ❒ Once a month or less

5. On average, how often is your bedroom aired by opening windows for at least for 1-hour? (*Tick one)*

- ❒ 5 or more times each week
- ❒ 2-4 times each week
- ❒ Once a week
- ❒ Less than once a week but more than once a month
- ❒ Once a month or less

6. Which types of **heating do you use at home**? *(Tick all that apply)*

- ❒ Gas ducted central heating
- ❒ Coal or wood fire
- ❒ Gas room heater
- ❒ Electric heater (eg: radiator, fan or Dimplex type)
- ❒ Other central heating (eg: electric hydronic, slab floor)
- ❒ Reverse cycle air-conditioning
- ❒ Other? Specify _____

7. What kind of stove do you mostly use for cooking?

- ❒ Gas
- ❒ Electric
- ❒ Coal, coke or wood
- ❒ Other? Specify _____

7.1 Do you have an exhaust fan over the stove? ❒ No ❒ Yes

If no, go to Q8

If yes ☞ 7.2 When cooking how often do you use the fan?

- ❒ All of the time
- ❒ Some of the time
- ❒ None of the time

7.3 Does the fan take the fumes outside the house? ❒ No ❒ Yes

8. Has there ever been mould or mildew on any surface, other than food, in your home? ❒ No ❒ Yes

If no, go to Q9

If yes ☞ 8.1 Which rooms have been affected?

- ❒ Bathrooms
- ❒ Living rooms
- ❒ Your bedroom
- ❒ Kitchen
- ❒ Other bedrooms
- ❒ Any other area/s

8.2 Has there ever been mould or mildew on any surface, other than food, in your home in the last 12 months? ❒ No ❒ Yes

9. Do you keep or own any cats? ❒ No ❒ Yes

If no, go to Q10

If yes ☞ 9.1 How many? Number ☐☐

9.2 Are the cats **allowed** indoors? ❒ No ❒ Yes

If no, go to Q10

If yes ☞ 9.2.1 Are the cats **allowed** in the bedroom? ❒ No ❒ Yes

10. Has there been a cat in the house in the last 12 months? ❒ No ❒ Yes ❒ DK

11. Do you keep or own any dogs? ❒ No ❒ Yes

If no, go to Q12

If yes ☞ 11.1 How many? Number ☐☐

11.2 Are the dogs **allowed** indoors? ❒ No ❒ Yes

If no, go to Q12

If yes ☞ 11.2.1 Are the dogs **allowed** in the bedroom? ❒ No ❒ Yes

12. Has there been a dog in the house in the last 12 months? ❒ No ❒ Yes ❒ DK

CHILDHOOD ENVIRONMENT

13. What term best describes the place you lived most of the time when you were under the age of five years? *Tick one*

❒ Farm
❒ Country town
❒ Suburb of a city
❒ Inner city
❒ Don't know

14. How many of your brothers, sisters or other children regularly slept in your bedroom before you were five years old, not including yourself?

☐☐ (number of sibs)

15. Did you have a serious respiratory infection before the age of five years?

❒ No ❒ Yes

16. Did you go to school, pre-school, kindergarten, or a day care centre before the age of five years?

❒ No ❒ Yes

17. <u>At what age did you first attend a school, pre-school, kindergarten, or day care?</u>

☐☐ (age in years)

18. Did your f<u>ather smoke</u>:

During the first year of your life? ❒ No ❒ Yes ❒ DK
When you were aged 1-4 years? ❒ No ❒ Yes ❒ DK
When you were aged 5-15 years? ❒ No ❒ Yes ❒ DK

19. Did your <u>mother smoke</u>:

During the first year of your life? ❒ No ❒ Yes ❒ DK
When you were aged 1-4 years? ❒ No ❒ Yes ❒ DK
When you were aged 5-15 years? ❒ No ❒ Yes ❒ DK

20. Was there a cat in your home:

During the first year of your life? ❒ No ❒ Yes ❒ DK
When you were aged 1-4 years? ❒ No ❒ Yes ❒ DK
When you were aged 5-15 years? ❒ No ❒ Yes ❒ DK

21. Did you have <u>carpet (or a rug) covering the floor in your bedroom</u>:

During the first year of your life? ❒ No ❒ Yes ❒ DK
When you were aged 1-4 years? ❒ No ❒ Yes ❒ DK
When you were aged 5-15 years? ❒ No ❒ Yes ❒ DK

22. What was the main type of heating your home had when you were under the age of five years? (tick all that apply)

- ❒ Gas ducted central heating
- ❒ Coal or wood fire
- ❒ Gas room heater
- ❒ Electric heater (eg. Radiator, fan or dimplex-type)
- ❒ Other central heating (eg. Electric, hydronic, slab floor)
- ❒ Reverse cycle air-conditioning
- ❒ Other
- ❒ No heating

SMOKING

23. In your lifetime, have you smoked at least 100 cigarettes or equal amounts of cigars, pipes or any tobacco product?

❒ No ❒ Yes

If no, go to Q24

If yes ☞ 23.1 How old were you when you started smoking? ☐☐ (Age in years)

23.2 Do you currently smoke (within the last 4 weeks)?

- ❒ Not at all ☞ Go to Q23.4
- ❒ Yes, daily ☞ Go to Q 23.3
- ❒ Yes, at least weekly ☞ Go to Q 23.3
- ❒ Yes, less than weekly ☞ Go to Q 23.3

23.3 On average, how much do you currently smoke (total number of cigarettes or equivalent product)? *Provide the average number per day or per week or per month*

☐☐ per day ☞ Go to Q24
or
☐☐ per week ☞ Go to Q24
or
☐☐ per month ☞ Go to Q24

23.4 How old were you when you stopped smoking? ☐☐ (Age in years)

23.5 On average, during periods when you smoked, how much did you smoke (total number of cigarettes or equivalent product)? *Provide the average number per day or per week or per month*

☐☐ per day

or

☐☐ per week
or
☐☐ per month

24. Not counting yourself, how many people in your household currently smoke regularly (most days of the week) inside the house? (number) ☐☐

25. On average, how many hours per day are you exposed to other people's tobacco smoke (work and home)? (hours per day) ☐☐

RESPIRATORY AND ALLERGY SYMPTOMS

ECZEMA

26. Have you ever had eczema or any kind of skin allergy? ❒ No ❒ Yes

27. Have you ever had an itchy rash that was coming and going for at least 6 months? ❒ No ❒ Yes

If yes ☞ 27.1 How old were you when you first had this itchy rash? ☐☐ (Age in years)

27.2 Have you had this itchy rash in the last 12 months? ❒ No ❒ Yes

27.3 Has this rash at any time affected any of the following places: *(tick all that apply)*

- ❒ Folds of the elbows
- ❒ Behind the knees
- ❒ In front of the ankles
- ❒ Under the buttocks
- ❒ Around the neck, ears or eyes
- ❒ None of the above

HAY FEVER

28. Have you ever had hay fever or nasal allergies (that is sneezing, running or blocked nose when you do not have a cold or the flu)? ❒ No ❒ Yes

If yes ☞ 28.1 Have you had this problem in the last 12 months? ❒ No ❒ Yes

28.2 Was this problem accompanied by itchy or watery eyes?

❒ No ❒ Yes

28.3 How old were you when you first had hayfever or nasal allergies?

☐☐ (Age in years)

29. When you are near animals, such as cats, dogs, or horses; near feathers, including pillows, quilts or doonas; or in a dusty part of the house, do you ever: (*tick all that apply*)

- ❒ Start to cough?
- ❒ Start to wheeze?
- ❒ Get a feeling of tightness in the chest?
- ❒ Start to feel short of breath?
- ❒ Get a runny or stuffy nose or start to sneeze?
- ❒ Get itchy or watery eyes?

30. When you are near trees, grass or flowers, or when there is a lot of pollen about, do you ever:

- ❒ Start to cough?
- ❒ Start to wheeze?
- ❒ Get a feeling of tightness in the chest?
- ❒ Start to feel short of breath?
- ❒ Get a runny or stuffy nose or start to sneeze?
- ❒ Get itchy or watery eyes?

If yes to any of the above☞ 30.1 At which time of the year does this happen?

- ❒ Winter
- ❒ Spring
- ❒ Summer
- ❒ Autumn

FOOD ALLERGY

31. Have you ever had any food allergies? ❒ No ❒ Yes

If yes ☞

	Peanut	Tree nut	Shellfish	Fish	Cow's milk	Egg	Wheat*	Sesame	Other
What food?									
Was it confirmed by a doctor?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
What age did you develop it? (years)	____	____	____	____	____	____	____	____	____
Are you still allergic to it?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Have you been prescribed an Epipen?	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
Specify the name/s of Tree Nut or other food if relevant		____							____

*include Coeliac disease

RESPIRATORY AND SLEEP CONDITIONS

32. Have you, at anytime in your life, suffered from attacks of asthma of wheezy breathing? (Regard asthma and wheezy breathing as being much the same thing for this question.)

❒ No ❒ Yes

If yes ☞ 32.1 How old were you when you had your first attack of asthma or wheezy breathing? ☐☐ *(age in years)*

32.2 How old were you when you had your most recent attack of asthma or wheezy breathing? ☐☐ *(age in years)*

32.3 Have you had an attack of asthma or wheezy breathing in the last 12 months? ❒ No ❒ Yes

32.4 Have you taken any medicines including inhalers or tablets for asthma or wheezy breathing in the last 12 months? ❒ No ❒ Yes

33. Have you had wheezing or whistling in your chest in the last 12 months?
(Wheezing means a whistling sound, however high or low pitched and however faint.)

❒ No ❒ Yes

If yes ☞ 33.1 Have you been at all breathless when the wheezing noise was present? ❒ No ❒ Yes

33.2 Have you had this wheezing or whistling when you did not have a cold? ❒ No ❒ Yes

34. Have you, at any time in the last 12 months, had an attack of shortness of breath at rest? ❒ No ❒ Yes

35. Have you, at any time in the last 12 months, had an attack of shortness of breath after exercise? ❒ No ❒ Yes

36. Have you, at any time in the last 12 months, woken due to a feeling of tightness in your chest? ❒ No ❒ Yes

36.1 During the last month, do you or have you been told you snore loudly in sleep? ❒ No ❒ Yes ❒ Don't know

If yes ☞ 36.1.1 On average, how often? *Tick one*☑

- ❒ Rarely, less than once a week
- ❒ 1 – 2 times per week
- ❒ 3 – 4 times per week
- ❒ 5 – 7 times per week
- ❒ Don't know

36.2 During the last month, do you or have you been told you snort or gasp in sleep? ❒ No ❒ Yes ❒ Don't know

If yes ☞ 36.2.1 On average, how often? *Tick one*☑

- ❒ Rarely, less than once a week
- ❒ 1 – 2 times per week
- ❒ 3 – 4 times per week
- ❒ 5 – 7 times per week
- ❒ Don't know

36.3 During the last month, do you or have you been told you choke or stop breathing in sleep? ❒ No ❒ Yes ❒ Don't know

If yes ☞ 36.3.1 On average, how often? *Tick one*☑

- ❒ Rarely, less than once a week
- ❒ 1 – 2 times per week
- ❒ 3 – 4 times per week
- ❒ 5 – 7 times per week
- ❒ Don't know

36.4 During the last month, have you had excessive sleepiness during the day? ❒ No ❒ Yes

37. Have you, at any time in the last 12 months, been woken at night by an attack of shortness of breath? ❒ No ❒ Yes

38. Do you usually cough when you do not have a cold? ❒ No ❒ Yes

If yes ☞ 38.1 Are there months in which you cough on most days? ❒ No ❒ Yes

If yes ☞ 38.1.1 Do you cough on most days for at least three months of each year? ❒ No ❒ Yes

38.1.2 For how many years have you had this cough?

- ❒ Less than 2 years
- ❒ 2 – 5 years
- ❒ More than 5 years

39. Do you usually have phlegm in your chest when you do not have a cold? ❒ No ❒ Yes

If yes ☞ 39.1 Are there months in which you have phlegm in your chest on most days? ❒ No ❒ Yes

If yes ☞ 39.1.1 Do you bring up this phlegm on most days for at least three months of each year? ❒ No ❒ Yes

39.1.2 For how many years have you had this phlegm?

- ❒ Less than 2 years
- ❒ 2 – 5 years
- ❒ More than 5 years

40. Have you, at anytime in your life, suffered from cough with phlegm in the chest (with or without a cold)? ❒ No ❒ Yes

If yes ☞ 40.1 Have you had this cough with phlegm on most days for at least three months and for two years in a row? ❒ No ❒ Yes

41. Have you at any time in your life suffered from attacks of bronchitis or attacks of cough with sputum (phlegm) in the chest ("loose" or "rattly" cough)? ❒ No ❒ Yes

If yes ☞ 41.1 How long is it since the last attack

- ❒<=6months
- ❒<=1 year but > 6 months
- ❒<=2 years but > 1 year
- ❒> 2 years

41.2 At what age did these attacks begin? ☐☐ *(age in years)*

42. Has your doctor ever told you that you have or had chronic bronchitis?

❒ No ❒ Yes

If yes ☞ 42.1 How old were you when you were told you had chronic bronchitis? ☐☐ *(age in years)*

42.2 Have you taken any medicine (including inhalers or tablets) for chronic bronchitis in the last three months?

❒ No ❒ Yes

43. Has your doctor ever told you that you have or had emphysema?

❒ No ❒ Yes

If yes ☞ 43.1 How old were you when you were told you had emphysema? ☐☐ *(age in years)*

43.2 Have you taken any medicine (including inhalers or tablets) for emphysema in the last three months?

❒ No ❒ Yes

44. Has your doctor ever told you that you have or had chronic obstructive pulmonary disease (COPD) or chronic obstructive airways disease (COAD)?

❒ No ❒ Yes

If yes ☞ 44.1 How old were you when you were told you had chronic obstructive pulmonary disease? ☐☐ *(age in years)*

44.2 Have you taken any medicine (including inhalers or tablets) for chronic obstructive pulmonary disease in the last three months?

❒ No ❒ Yes

45. Has your doctor ever told you that you have or had obstructive sleep apnoea?

❒ No ❒ Yes

If yes ☞ 45.1 How old were you when you were told you had obstructive sleep apnoea? ☐☐ *(age in years)*

45.2 Are you currently being treated for obstructive sleep apnoea with CPAP, surgery, adequate weight loss or other device?

❒ No ❒ Yes

CHEST COLDS AND CHEST ILLNESSES

46. If you get a cold, does it usually go to your chest? (Usually means more than half of the time) ❒ No ❒ Yes ❒ Do not get colds

47. During the past 3 years, have you had any chest illnesses that have kept you off work, indoors at home, or in bed? ❒ No ❒ Yes

If yes ☞ 47.1 Did you produce phlegm with any of the chest illnesses? ❒ No ❒ Yes

47.2. In the last 3 years, how many such illnesses, with increased phlegm, did you have which lasted a week or more? (if none enter zero)

Number of illnesses ☐☐

48. Have you ever had Pneumonia? ❒ No ❒ Yes

If yes ☞ 48.1 Was this confirmed by a doctor? ❒ No ❒ Yes

48.2 At what age did you first have it? ☐☐ Age in *years*

48.3 How many times have you had it? ☐☐ number

48.4 Have you ever been hospitalised for Pneumonia? ❒ No ❒ Yes

49. Have you ever been hospitalised for any other chest illness? ❒ No ❒ Yes

If yes ☞ please specify

	Diagnosis	Age at first occurrence	No. occurrences
1			
2			
3			

ASTHMA

Now I am going to ask few detailed questions about asthma that you may or may not have.

50. Have you ever had asthma ? ❒ No ❒ Yes

If no, go to Q51

If yes continue

50.1 How old were you when you had your first symptoms of asthma? (Age in years) ☐☐

50.2 Was this confirmed by a doctor? ❒ No ❒ Yes

If yes 50.2 How old were you when this was confirmed? ☐☐ *years old*

50.3 How old were you when you had your most recent symptoms of asthma? *years old* ☐☐

Symptom Severity

50.4. Have you been woken from your sleep by your asthma?

last 12 months		*last 1 month*	
❒ No	❒ Yes	❒ No	❒ Yes

If Yes to last month:

49.4.1 How many nights were you woken from sleep by your asthma the last week?

☐☐ *No. of nights*

50.5. Have you had asthma symptoms when you wake in the morning?

last 12 months		*last 1 month*	
❒ No	❒ Yes	❒ No	❒ Yes

If Yes to last month:

50.5.1 How many mornings in the last week? ☐☐ *No. of mornings*

50.6 Have you been limited in any of the following activities because of asthma?

Tick the appropriate boxes in each category:

	last 12 months		*last 1 month*	
50.6.1 All activities	❒ No	❒ Yes	❒ No	❒ Yes
50.6.2 When dressing	❒ No	❒ Yes	❒ No	❒ Yes
50.6.3 Walking on level ground	❒ No	❒ Yes	❒ No	❒ Yes
50.6.4 Hurrying on level ground	❒ No	❒ Yes	❒ No	❒ Yes
50.6.5 Walking up stairs or up hills	❒ No	❒ Yes	❒ No	❒ Yes
50.6.6 Active sports	❒ No	❒ Yes	❒ No	❒ Yes
50.6.7 Other (Specify) _____	❒ No	❒ Yes	❒ No	❒ Yes

☞ *If Yes to any of* 50*.6.1 to* 50*.6.7, go to* 50*.7.*
If all were No, answer 50*.6.8 first.*

50.6.8 Would you agree or disagree with the following statement:

"My asthma has not limited any of my activities."

last 12 months		*last month*	
❒ agree	❒ disagree	❒ agree	❒ disagree

<u>50.7. How frequent have your asthma symptoms (of any severity) been?</u>

Tick one

- ❒ No asthma in the past 12 months
- ❒ Asthma symptoms in the past 12 months but not in the last month
- ❒ Asthma symptoms in the last month, but not frequent (less than once per week)
- ❒ Frequent (once per week or more but not daily) in the last 1 month
- ❒ Persistent (daily)

☞ *If 'No asthma in the past 12 months', go to* 50*.14. If any asthma in last 12 months continue*

50.8. How frequent have your asthma attacks/flare ups been over the past 12 months?

An "attack" or "flare up" of asthma is a period of time when asthma symptoms are worse or more frequent than usual. One could have asthma symptoms regularly or intermittently without getting attacks or flare-ups.

Tick one

- ❒ None in the past 12 months
- ❒ 3 or less in the past 12 months
- ❒ 4 or more but less than monthly
- ❒ More than monthly in the last 12 months
- ❒ More than weekly or persistent
- ❒ Not sure

50.9. Have you had an episode of asthma which has made you unable to speak or severe enough to limit your speech to only 1 or 2 words between breaths?

last 12 months		*last 1 month*	
❒	❒	❒	❒
No	Yes	No	Yes

50.10. On average, how would **you** rate the severity of your asthma?

	last 12 months tick one	*last 1 month tick one*
Not severe at all	❒	❒
Mild	❒	❒
Moderate	❒	❒
Severe	❒	❒
Not sure	❒	❒

Events

50.11. Have you lost any days from work, school or usual activities because of your asthma?

last 12 months		*last 1 month*	
❒	❒	❒	❒
No	Yes	No	Yes

If yes ☞: 50.11.1. How many? ☐☐ *last 12 months* ☐☐ *last 1 month*

50.12. Have you had an attack or symptoms of asthma that was so bad, you needed to call your general practitioner, ambulance, emergency locum or 24 hour clinic?

last 12 months		*last 1 month*	
❒	❒	❒	❒
No	Yes	No	Yes

If yes ☞ 50.12.1. How many? ☐☐ *last 12 months* ☐☐ *last 1 month*

50.13. Have you had an attack or symptoms of asthma that was so bad you had to go to a hospital emergency or casualty department?

	last 12 months		*last 1 month*	
	❒ No	❒ Yes	❒ No	❒ Yes
If yes ☞ 50.13.1. How many?	☐☐ *last 12 months*		☐☐ *last 1 month*	

50.14. Have you ever been admitted to a hospital because of your asthma? ❒ No ❒ Yes

✋ *If no, go to Q50.15*

If yes ☞ 50.14.1 In the past 12 months? ❒ No ❒ Yes

If yes ☞ 50.14.1.1 How many times in the last 12 months? ☐☐ *Number*

50.14.1.2 How many times in the last 1 month? ☐☐ *Number*

50.15. Have you ever had an attack or symptoms of asthma that resulted in an admission to a hospital intensive care unit? ❒ No ❒ Yes

50.15a How frequently have you seen the following health professionals for your asthma in the last 12 months? (enter zero if not at all)

1) General Practitioner (No. of times last 12 months) ☐☐ *Number*

2) Respiratory specialist (No. of times last 12 months) ☐☐ *Number*

3) Nurse/Asthma educator (No. of times last 12 months) ☐☐ *Number*

4) Pharmacist (No. of times last 12 months) ☐☐ *Number*

50.16 Have you ever been given a demonstration on the correct use of your metered dose inhaler? ❒ No ❒ Yes

If yes 50.16.1 In the last 12 months? ..... ❒ No ❒ Yes

50.17 Has your doctor ever checked your inhaler technique? ❒ No ❒ Yes

If yes 50.17.1 In the last 12 months? ..... ❒ No ❒ Yes

50.18 Do you have written instructions from your doctor on how to manage your asthma if it gets worse or if you have an attack?
..... ❒ No ❒ Yes

If yes 50.18.1 In the last 12 months? ..... ❒ No ❒ Yes

50.19 Has your doctor given you a verbal plan telling you how to manage your asthma if it gets worse or if you have an attack?
..... ❒ No ❒ Yes

If yes 50.19.1 In the last 12 months? ..... ❒ No ❒ Yes

50.20 Do you have a peak flow meter of your own? ..... ❒ No ❒ Yes

If yes 50.20.1 How often have you used it in the last 3 months?

A) Never ❒
B) Some days ❒
C) Most days ❒

50.21 Has your doctor ever measured your breathing in his/her surgery (including peak flows/spirometry/bronchodilator response)? ..... ❒ No ❒ Yes

If yes 50.21.1 In the last 12 months? ..... ❒ No ❒ Yes

FAMILY PREDISPOSITION

I am now going to ask about the respiratory conditions of your family members. It is possible that you are not aware of these details but respond according to what you know about your family.

51. Has your biological mother ever had self reported or doctor diagnosed:

51.1 Asthma? ❒ No ❒ Yes ❒ Don't know

51.2 COPD, COAD, chronic bronchitis or emphysema? ❒ ❒ ❒

No Yes Don't know

52. Has your biological father ever had self reported or doctor diagnosed:

52.1 Asthma? ❒ No ❒ Yes ❒ Don't know

52.2 COPD, COAD, chronic bronchitis or emphysema? ❒ No ❒ Yes ❒ Don't know

53. Do you, or did you, have any biological brothers or sisters? This includes half-brothers and half-sisters, but not step-brothers or step-sisters. ❒ No ❒ Yes ❒ Don't know

If No, go to Q54

If yes ☞ 53.1 How many? ☐☐ Number ❒ Don't know

53.2 How many of your biological brothers or sisters have ever had self reported or doctor diagnosed:

53.2.1 Asthma? ☐☐ Number ❒ Don't know

53.2.2 COPD, COAD, chronic bronchitis, emphysema? ☐☐ Number ❒ Don't know

54. Do you, or did you, have any biological children? ❒ No ❒ Yes

If No, go to Q54 *If Yes continue*

53.1 How many? ☐☐ Number

53.2. How many of them have ever had self reported or doctor diagnosed asthma? ☐☐ Number ❒ Don't know

55. Has any member of your family or close relatives died from asthma? By family and close relatives I mean children, parents, siblings, nephews, nieces, grand parents, first cousins, uncles and aunts ❒ No ❒ Yes ❒ Don't know

If Yes: 55.1 How many? ☐☐ Number

56. Has any member of your family or close relatives died from COPD/COAD/Chronic Bronchitis/Emphysema?

❒ No ❒ Yes ❒ Don't know

If Yes: 56.1 How many? ☐☐

Number

When administering Q57 and Q58:
First ask the main question as given below i.e. "Have you used any inhaled medicines to help your breathing in the last 12 months?"
If the response is yes, get the participant to tell what medication/s he/she has used and find what group of drugs the participant's drug belongs to from the medication list provided with this questionnaire.
Then administer the sub questions under each medication (i.e. if a ***Short Acting beta-2-agonist inhaler is used complete 57.1 to 57.1.2)***

MEDICINES AND INHALERS

57. Have you used any inhaled medicines to help your breathing in the last 12 months? ❒ No ❒ Yes

If No, go to Q58. If Yes, continue - **Which have been used in the last 12 months?**

	Medication 1	Medication 2	Medication 3	Medication 4
57.1 Which one?				
57.2 Which type of inhaler device?				
57.3 Strength/dose per puff (mcg)?				
57.4Are you currently using this medication?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
57.5 how long have you been using this med?	_ _ _ _ Days/Mths/Yrs	_ _ _ _ Days/Mths/Yrs	_ _ _ _ Days/Mths/Yrs	_ _ _ _ Days/Mths/Yrs
57.6 Last 12mths, how have you used them:				
57.6a) when needed - Average number of puffs per month	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)
57.6b) in short courses -Number of courses in last 12 months -Average number of puffs per day during flare-up -Average number of days of flare-up	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)
57.6c) continuously - Average number of puffs per day	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)
57.6d) not at all	□	□	□	□
57.7 Last 1mth, how have you used them:				
57.7a) when needed - Average number of puffs per month	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)
57.7b) in short courses -Number of courses in last 12 months -Average number of puffs per day during flare-up -Average number of days of flare-up	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (puff/day) _ _ _ _ (days)
57.7c) continuously - Average number of puffs per day	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)
57.7d) not at all	□	□	□	□
57.8) Is this medication the same type as prescribed by your doctor?	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK
57.9) Are you taking this medication at the same dose as prescribed by your doctor?	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK
57.9a) If no to Q57.8 or Q57.9 why not the same: (tick all that apply)	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____

58. Have you used any pills, capsules, tablets or medicines, other than inhaled medicines to help your breathing at any time in the last 12 months? ❒ No ❒ Yes

☞ *If No go to Q 59, if Yes continue* - **Which have been used in the last 12 months?**

	Medication 1	Medication 2	Medication 3	Medication 4
58.1 Which one?				
58.2 Strength/dose per tablet (mg)?				
58.3 Are you currently using this medication?	□ Yes □ No	□ Yes □ No	□ Yes □ No	□ Yes □ No
58.4 how long have you been using this med?	_ _ _ _ Days/Mths/Yrs	_ _ _ _ Days/Mths/Yrs	_ _ _ _ Days/Mths/Yrs	_ _ _ _ Days/Mths/Yrs
58.5 Last 12mths, how have you used them:				
58.5a) when needed - Average number of tablets per month	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)
58.5b) in short courses - Number of courses in last 12 months - Number of tablets per day during flare-up - Average number of days of flare-up	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)
58.5c) continuously - Average number of puffs per day	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)
58.5d) not at all	□	□	□	□
58.6 Last 1mth, how have you used them:				
58.6a) when needed - Average number of puffs per month	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)	_ _ _ _ (puff/mth)
58.6b) in short courses - Number of courses in last 12 months - Average number of tablets per day during flare-up - Average number of days of flare-up	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)	_ _ _ _ (number) _ _ _ _ (tablets/day) _ _ _ _ (days)
58.6c) continuously - Average number of puffs per day	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)	_ _ _ _ (puffs)
58.6d) not at all	□	□	□	□
58.7) Is this medication the same type as prescribed by your doctor?	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK
58.8) Are you taking this medication at the same dose as prescribed by your doctor?	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK	□ Yes □ No □ DK
58.8a) If no to Q58.7 or Q58.8 why not the same: (tick all that apply)	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____	□ Cost □Side effects □ Symptoms resolved □ forget to take □ Other?Specify _____

59. Have you ever used inhaled steroids to help your breathing? ❒ No ❒ Yes

If No go to Q 59, if Yes continue

59.1 At what age did you start using inhaled steroids? ☐☐ years

59.2 In the past 5 years, how many months would you have used inhaled steroids on most days? ☐☐ months

60. Have you ever been prescribed home oxygen therapy? ❒ No ❒ Yes

If no go to Q60. If Yes continue

60.1 Are you currently using oxygen therapy at home? ❒ No ❒ Yes

60.2 For how many years have you been using oxygen therapy at home? ☐☐ Years

60.3 How have you used oxygen therapy during the last month?

60.3.1 For relief of symptoms or when needed ❒ No ❒ Yes

60.3.2 For flare-ups or attacks ❒ No ❒ Yes

60.3.3 Regularly, on a daily basis ❒ No ❒ Yes

61. Have you ever had an influenza vaccination? ❒ No ❒ Yes

If yes: 61.1 Have you been vaccinated for influenza in the last 12months? ❒ No ❒ Yes

62. Have you ever had a pneumonia vaccination? ❒ No ❒ Yes

If yes: 62.1 Have you been vaccinated for pneumonia in the last 5 years? ❒ No ❒ Yes

63. Have you ever been vaccinated or desensitised for allergy? ❒ No ❒ Yes

If yes: 63.1 Have you been vaccinated for allergy in the last 12 months? ❒ No ❒ Yes

64. Have you had any other injections to help your breathing at any time in the last 12 months? ❒ No ❒ Yes

If yes: 64.1 what injections? _____

OTHER CONDITIONS

65. Has a doctor ever told you that you have/had any of the following conditions?

- ❒ Angina, heart attack or myocardial infarction
- ❒ Transient ischaemic attack (TIA) or a stroke
- ❒ High blood pressure or Hypertension
- ❒ High levels of cholesterol/ triglycerides
- ❒ Diabetes or high sugar levels in the blood or urine
- ❒ Cancer
- ❒ Rheumatoid arthritis
- ❒ Psychiatric/ mental health problem
- ❒ Multiple Sclerosis
- ❒ Thyroid Problems
- ❒ Lupus/ Systemic Lupus Erythematosus

If FEMALE please continue ……
If MALE thank you for your assistance with this Questionnaire

FEMALES ONLY

66. Have you ever had a menstrual period? ❒ No ❒ Yes

If yes: 66.1 What was your age when you had your first period? ☐☐ (age in years)

66.2 Have you had a menstrual period in the last 12 months?
- ❒ No ☞ Go to 66.3
- ❒ Yes ☞ Go to 67
- ❒ Don't know ☞ Go to 67

66.3 Have your menstrual periods stopped permanently or only temporarily due to pregnancy, breast feeding or other condition?
- ❒ Stopped permanently ☞ continue
- ❒ Stopped temporarily ☞ Go to 67

66.4 How old were you when your periods stopped permanently? ☐☐ *(age in years)*

67. Have you ever used birth control pills or other hormonal contraceptives (implants or injections)? ❒ No ❒ Yes

If yes: 67.1 At what age did you first use birth control pills or other hormonal contraceptives? (age in years) ☐☐

67.2 Are you currently taking birth control pills or other hormonal contraceptives? ❒ No ☐ Yes

67.3 Over your whole lifetime, in total how many months or years have you taken birth control pills or other hormonal contraceptives?

☐☐ Months OR ☐☐ Years

68. Are you currently pregnant? ❒ No ❒ Yes

69. Have you ever been pregnant in the past? ❒ No ❒ Yes

70. How many live births have you had? ☐☐

71. How many miscarriages or abortions have you had? ☐☐

72. Have you ever had a mammogram? ❒ No ❒ Yes

73. Have you ever taken oestrogen, progesterone or other female hormones for menopause (that is, prescription hormone replacement therapy or HRT)?

The preparation may be pills, injections or skin patches. This question does not include birth control pill or hormonal contraceptives. ❒ No ❒ Yes

If yes, complete HRT section

Thank you for your assistance with this Questionnaire

Appendix 8- Reports on Reuters Health



#HEALTH NEWS JULY 29, 2017 / 6:29 AM / 13 DAYS AGO

Occupational pesticide and herbicide exposure tied to lung disease

Lisa Rapaport 4 MIN READ

(Reuters Health) - Workers exposed to pesticides and herbicides on the job may be more likely than other people to develop chronic obstructive pulmonary disease (COPD), bronchitis and other breathing problems, an Australian study suggests.

With any herbicide exposure at work, people were more than twice as likely to develop COPD by middle age, and workplace pesticide exposure was associated with 74 percent higher odds of the common lung disease, researchers report in Thorax.

Over a lifetime, pesticides and herbicides may pose an even bigger added risk for breathing disorders, the study also found.

Each ten-year increase in occupational exposure to pesticides carried a 12 percent increased risk of COPD and a 16 percent higher risk of developing chronic bronchitis. Every extra decade of herbicide exposure, meanwhile, carried a 22 percent increased risk of bronchitis, while each ten years of insecticide exposure was associated with 15 percent higher odds of bronchitis.

"Our study looked at long-term exposure to pesticides, and it is thought that long-term exposure to pesticides increases mucus secretion and muscle contraction in the lungs, causing breathlessness, cough and wheeze," lead study author Dr. Sheikh Alif of the University of Melbourne in Australia said by email.

Globally, more than 65 million people have moderate to severe COPD, and the condition causes about 5 percent of all deaths, according to the World Health

Organization (WHO).

Most cases are caused by smoking or exposure to second-hand smoke, but working or cooking around certain toxic dusts, chemicals and fuels can also contribute, as can frequent respiratory infections during childhood.

For the current study, researchers examined data collected on 1,335 workers from 2002 to 2008, including information on workplace exposure to pollutants as well as results from breathing tests to detect COPD and other respiratory issues.

Study participants were 45 year old on average, 87 percent were currently employed and 25 percent were current smokers.

Overall, 6 percent of them had COPD, 8.6 percent had chronic bronchitis, and more than 28 percent reported having asthma currently or previously.

In addition to risks associated with pesticides and herbicides, the study also found workers who didn't have asthma had an increased risk of COPD when they had any exposure to toxic mineral dust, gases, fumes and vapors. There didn't appear to be an association between exposure to these pollutants and COPD in people with asthma, however.

The study wasn't a controlled experiment designed to prove whether or how exposure to pollutants at work might contribute to COPD, bronchitis or other breathing problems.

"We can not make firm conclusions about the extent of exposure needed to cause changes in lung function," said Dr. Steve Georas, an environmental health researcher at the University of Rochester in New York who wasn't involved in the study.

"We know that single exposures to high levels of some toxicants can cause long lasting changes in airway function (i.e. chlorine gas)," Georas said by email. "I suspect that for pesticides and herbicides, long-term low level exposure may be more important, but this is speculation."

SOURCE: bit.ly/2eUSS9j Thorax, online July 7, 2017.