University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Zhang, J;Lodge, CJ;Walters, H;Chang, AB;Bui, DS;Lowe, AJ;Hamilton, GS;Thomas, PS;Senaratna, CV;James, AL;Thompson, BR;Erbas, B;Abramson, MJ;Perret, JL;Dharmage, SC

Title:
Association of novel adult cough subclasses with clinical characteristics and lung function across six decades of life in a prospective, community-based cohort in Australia: an analysis of the Tasmanian Longitudinal Health Study (TAHS)

Date:
2024-02

Citation:
Zhang, J., Lodge, C. J., Walters, H., Chang, A. B., Bui, D. S., Lowe, A. J., Hamilton, G. S., Thomas, P. S., Senaratna, C. V., James, A. L., Thompson, B. R., Erbas, B., Abramson, M. J., Perret, J. L. & Dharmage, S. C. (2024). Association of novel adult cough subclasses with clinical characteristics and lung function across six decades of life in a prospective, community-based cohort in Australia: an analysis of the Tasmanian Longitudinal Health Study (TAHS). The Lancet Respiratory Medicine, 12 (2), pp.129-140. https://doi.org/10.1016/S2213-2600(23)00340-5.

Persistent Link:
https://hdl.handle.net/11343/340287

Association of novel adult cough subclasses with six decades of clinical characteristics and lung function in a prospective cohort (TAHS)

Authors:

Jingwen Zhang (MPH)[1], Caroline J. Lodge (PhD)[1], E. Haydn Walters (DM, Prof)[1,2], Anne B. Chang (PhD, Prof)[3,4], Dinh S. Bui (PhD)[1], Adrian J. Lowe (PhD, Prof)[1,5], Garun S. Hamilton (PhD, Prof)[6,7], Paul S. Thomas (PhD, Prof)[8], Chamara V. Senaranta (PhD)[1], Alan L. James (PhD, Prof)[9,10], Bruce R. Thompson (PhD, Prof)[11], Bircan Erbas (PhD, Prof)[12], Michael J. Abramson (PhD, Prof)[13], Jennifer L. Perret (PhD)[1,14*], Shyamali C. Dharmage (PhD, Prof)[1*]

Affiliations:

[1]Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, VIC, Australia.

[2]School of Medicine, University of Tasmania, TAS, Australia

[3]Australian Centre for Health Services Innovation, Queensland University of Technology, QLD, Australia

[4]Child Health Division, Menzies School of Health Research, NT, Australia

[5]Murdoch Children's Research Institute

[6]Monash Lung, Sleep, Allergy & Immunology, Monash Health, VIC, Australia

[7]School of Clinical Sciences, Monash University, VIC, Australia

[8]Prince of Wales' Clinical School UNSW and Respiratory Medicine, Prince of Wales' Hospital, Randwick, NSW 2031 Australia

[9]Department of Pulmonary Physiology and Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, WA, Australia

[10] School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

[11]Melbourne School of Health Sciences, The University of Melbourne, VIC, Australia

[12]School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia

[13]School of Public Health & Preventive Medicine, Monash University, Melbourne, VIC, Australia

[14]Institute for Breathing and Sleep, Heidelberg, VIC, Australia

*Equal Senior authors

Corresponding Author:

Professor Shyamali Dharmage, Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne,

207 Bouverie Street, Carlton, VIC 3053, Australia.

Tel: +61 3 83440737, Fax: +61 3 9349 5815

E-mail: s.dharmage@unimelb.edu.au

Panel: Research in context

Evidence before this study

Cough is a heterogenous condition. Yet, little is known about cough phenotypes. In clinical practice, cough phenotype is determined by its duration as well as the underlying diseases causing the cough. Conversely, in adults with chronic cough, a concept of cough hypersensitivity syndrome (CHS) has been proposed to encompass chronic cough featuring a hypersensitive cough reflex, regardless of the underlying diseases. However, the clinical presentations, especially responses to treatments, within each cough phenotype (or CHS) are still heterogeneous. We hypothesised cough phenotypes or subclasses identified from community settings would further elucidate such heterogeneity, as cough is most commonly seen in the community, while only a small group of people visit specialists because of their cough. We searched PubMed up to 2023, for articles on adult chronic cough phenotypes using the search terms “chronic cough” and “phenotype”. Most studies have been conducted in specialist clinical settings. Only two studies investigated cough phenotypes among community-based samples, and neither had data on lung function trajectories, nor longitudinal clinical characteristics since childhood.

Added value of this study

This is the first study to describe the longitudinal clinical characteristics of adult cough subclasses in a community-based cohort. We identified six mutually exclusive subclasses in middle-aged adults and have characterised them comprehensively by their history of respiratory symptoms, life-course lung function trajectories, and comorbidities. The two subclasses that featured “chronic productive” and “intermittent productive” cough had disadvantaged lung function trajectories, and a higher lifetime prevalence of productive cough, asthma, and allergies from as early as seven years of age. However, the “chronic dry cough” and “cough with allergies” subclasses showed such changes only in the mid-forties to fifties. These descriptions are a substantial advance of the current framework for understanding and managing chronic cough.

Implications of all the available evidence

For adults aged in their fifties, which is when the prevalence of chronic cough peaks, multiple subclasses of cough exist; each has distinct clinical features going back to childhood. Usual cough is common, and understanding the risk factors and comorbidity profiles specific to a cough subclass could inform personalised management focused on the patients’ “treatable traits”. Individuals

belonging to the more severe cough subclasses associated with phlegm, often have coughed from childhood, so vigilance by clinicians and closer monitoring for potential lung function impairment could provide opportunities for early intervention/prevention. Lung function should be routinely undertaken when evaluating and /or managing adults with productive cough including in primary care. This clinically relevant classification based on symptoms and objective lung function, and derived from a large general population cohort provides a platform for future studies to investigate the burden and optimal management of adults with chronic cough in the community.

ABSTRACT

Background: Cough is a common yet heterogeneous condition with poor understanding in general populations. We aimed to investigate cough subclasses, their lifetime characteristics, and treatable traits in a general population.

Methods: Using data collected by the Tasmanian Longitudinal Health Study (TAHS), we distinguished cough subclasses among current coughers at age 53 years, using latent class analysis of cough symptoms. Longitudinal changes and/or trajectories of cough, asthma, smoking, and spirometry from age 7 to 53 years for each subclass were documented and compared with the reference.

Findings: Six distinct cough subclasses were identified and labelled as "minimal cough" (n=206, 9%; the reference), "cough with colds only" (n=1189, 54%), "cough with allergies" (n=305, 14%), "intermittent productive cough" (n=213, 10%), "chronic dry cough" (n=147, 6%), and "chronic productive cough" (n=153, 7%). Compared to "minimal cough", the "chronic productive" and "intermittent productive" cough subclasses had worse lung function trajectories, and a higher prevalence of cough, asthma and allergies from ages 7 to 53 years. These differences were observed in other subclasses, but were evident only after their mid-forties in the groups with "chronic dry cough" and "cough with allergies" subclasses, and not until age 53 in the "cough with colds only" subclass.

Interpretation: Potential treatable traits were identified for different cough subclasses. Productive cough may require different management in primary care (i.e., routine spirometry) than dry cough, if our findings are confirmed by other studies. Future population-based studies could apply this framework to better address the heterogeneity and complexity of cough in the community.

Funding: National Health and Medical Research Council (NHMRC) of Australia; The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; Victorian, Queensland & Tasmanian Asthma Foundations; Royal Hobart Hospital; Helen MacPherson Smith Trust; GlaxoSmithKline, and China Scholarship Council (CSC).

INTRODUCTION

Cough is a common but difficult-to-treat condition;[1] yet it has substantial physical, mental, and economic impacts on patients, and the healthcare system.[2] Chronic cough in adults, defined as a daily cough for more than eight weeks, affects between 5% and 10% of the population globally.[3] Furthermore, studies have shown that chronic cough is an independent risk factor for cardiovascular disease and premature death.[4]

Cough is a heterogenous condition.[1] From a neurobiological perspective, multiple central and peripheral pathways are involved in the regulation of cough.[5] In clinical practice, cough can be caused by multiple underlying pulmonary and extrapulmonary diseases, and presentations of cough vary between diseases, and between patients with the same diseases.[1] The CHEST guidelines for adult cough recommend managing cough by diagnosing and treating underlying diseases, by firstly assessing the duration of the cough (i.e., whether it is acute, subacute, or chronic).[6] Earlier studies found that other features of cough (e.g., phlegm production, sound, timing) provide little guidance to diagnose underlying diseases.[7,8] Asthma, gastro-oesophageal reflux disease (GORD), and upper airway cough syndrome (UACS) are common underlying diseases causing chronic cough.[3,6] However, many patients with these diseases do not present with chronic cough.[1,3,6] In addition, treating these diseases does not necessarily resolve the cough.[1,3,6] Over 63% of people with chronic cough have two or more of these diseases, but 15% of them have no identified underlying diseases to explain the cough.[9] Furthermore, some of these underlying diseases are poorly defined in the first place (e.g., UACS).[3] Cough hypersensitivity syndrome has recently been proposed as an umbrella term to explain the mechanisms of chronic cough, regardless of underlying diseases. However, not all unexplained cough can be attributed just to hypersensitivity.[1] Together, these findings suggest that chronic cough is a complex and heterogeneous condition that cannot be fully explained by the "underlying diseases" or cough hypersensitivity.[1]

The "treatable trait", model of care where a patient undergoes a multidimensional assessment to identify clinically important and treatable problems (traits), has recently been introduced to the management of chronic airway diseases.[10] This approach emphasises using phenotypes and/or endotypes, instead of diagnostic labels, to guide individualised treatment.[10] However, little is known about adult cough phenotypes or endotypes in the general population. While few studies on adult cough phenotypes have been undertaken and they were mainly performed in specialist centres with

highly-selected patients,[11-13] even though cough is the most common reason people present to primary healthcare.[14] Furthermore, cough is very common in the community, but over 70% of all people with chronic cough have never consulted a doctor.[15] Only two studies have investigated adult cough phenotypes/subclasses in community settings,[9,16] but neither has linked these subclasses to potential treatable traits using longitudinal clinical characteristics.

Therefore, we aimed to explore cough subclasses in the general adult population, and to identify potentially treatable traits of the identified subclasses by describing their clinical characteristics from childhood to adulthood.

METHODS

Study Design and Data Collection

We used data from the Tasmanian Longitudinal Health Study (TAHS), a prospective community-based cohort study, following participants from ages 7 to 53 years (Figure 1). These individuals have been followed up at ages 13, 18, 31, 43, and 53 years with questionnaires and clinical examinations. Details about the study design and follow-up studies were published previously.[17]

During the most recent follow-up study in 2012-2016 (mean age 53 years), all surviving participants were traced and invited (n=6128). And 3609 (58.9%) of these returned a postal questionnaire. The questionnaire included nine cough-related questions (Table S1, supplements pp 2). Participants who answered "Yes" to at least one question were defined as "current coughers" at age 53 years, and; those who answered "No" to all nine questions were defined as "non-coughers".

Demographic and clinical characteristics of participants including asthma, smoking, and symptoms of cough ("current productive cough" and "ever chronic productive cough") have been collected via questionnaire from ages 7 to 53 years and the detailed definitions were harmonised and listed in Table S2 (supplements pp 3).

Pre-bronchodilator spirometry was performed at ages 7, 13, 18, 31, 45 and 53 years (Figure 1), according to the American Thoracic Society and European Respiratory Society guidelines.[18] Trajectories were developed previously (Appendix 1, supplements pp 11),[20] based on spirometry z-scores, which were derived from Global Lung Function Initiative (GLI) reference equations that have been validated in an Australian population.[19]

Statistical Analysis

The nine cough-related questions were included in latent class analysis (LCA) models as indicator variables among the "current coughers" (Table S1, supplements pp 2). The LCA estimated two sets of values: conditional probabilities (i.e., probability of having each of the nine cough and/or phlegm symptoms within a known class), and posterior probabilities (i.e., probability of belonging to each class for a given participant). Models were repeatedly fitted with a stepwise increase in the number of classes from 2 to 9. The LCA models with maximum likelihood estimation allowed for the handling of missing data for indicator variables, which were treated as missing at random. The Bayesian information criterion (BIC) and clinical interpretability of models were used as major criteria to determine the optimal number of classes. Class size, entropy and other statistics were also considered.[21] A single cough subclass was assigned to each participant based on the highest posterior probability for that participant from the six-class model and the mean posterior probability was used to assess model adequacy (Appendix 2, supplements pp 12-13; Figure S1, supplements pp 14).

Demographic and clinical characteristics of participants at age 53 years were described for each cough subclass and compared with the reference (defined as the "minimal cough" derived from the LCA), using χ^2, Fisher's exact tests, or independent t-tests where appropriate. Prevalence (p) and logit-transformed 95% confidence intervals (95%CI=expit {logit(p) ±1.96×standard error/[p×(1-p)]}) of relevant clinical characteristics (cough, asthma, smoking, asthma and allergy trajectories,[22] lung function trajectories[20]) were plotted from age 7 to age 53 years whenever data were available and compared with the "minimal cough" using χ^2 tests (or Fisher's exact tests). "Non-coughers" were compared with all identified cough subclasses. The above analyses were repeated using standard cough definitions (chronic cough [CC] as cough > three months regardless of the presence of phlegm; and chronic bronchitis [CB] as cough with phlegm > three months for two consecutive years). All analyses were done using Stata version 16 (Stata Corp, College Station, TX) with an LCA plug-in.[23]

Ethics

The study was approved by Human Review Committees at all participating institutions. Written informed consent was obtained from all participants.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit. The corresponding author had full access to all the data in the study and the final responsibility to submit for publication.

RESULTS

Among the 3609 participants of the most recent TAHS follow-up (mean age 53 years, Figure 1), 361 (10·0%) had standard definition CC, and 109 (3·0%) had standard definition CB. Altogether, 2213 (61·3%) participants were considered "current coughers" by having any kind of cough listed in Table S1 (supplements pp 2), and they were assigned to cough subclasses identified using latent class analysis (LCA). Based on model selection criteria, the six-class model was optimal (Appendix 2, supplements pp 12-13). The mean posterior probability of the six-class model was 0·9 suggesting good model adequacy in class assignment (Table S3, supplements pp 4). Conditional probabilities of having each cough and/or phlegm symptoms were presented in a Heatmap and used to label the six cough subclasses (Figure 2).

Characteristics of each cough subclass at age 53 years are summarised in Table 1. Participants with "minimal cough" (n=206, 9·3% of 2213 current coughers) had some cough with colds, but otherwise the lowest probabilities of all symptoms overall, and therefore comprised the reference group for the main analysis. The "cough with colds only" (n=1189, 53·7%) had moderate to high probabilities of symptoms related to colds/chest illness and the highest prevalence of recent respiratory infections. The "cough with allergies" (n=305, 13·8%) was predominantly female (66·9%), and had the highest probabilities of allergic symptoms and lowest prevalence of smoking. The "intermittent productive cough" (n=213, 9·6%) had moderate to high probabilities for symptoms with or without colds, productive cough of intermittent duration, and the highest mean BMI. The three major diseases related to chronic cough (asthma, GORD, chronic rhinosinusitis [CRS]) were most prevalent in the two chronic cough subclasses, namely "chronic dry cough" (n=147, 6·6%) and "chronic productive cough" (n=153, 6·9%). The "chronic productive cough" subclasses also had the highest prevalence of smoking, COPD, anxiety, and depression (Table 1, Figure 2).

177 The longitudinal clinical characteristics of 2213 current coughers from age 7 to 53 years were
178 described and compared in Figures 3-5, Figure S2 (supplements pp15), and Tables S4-S5
179 (supplements pp 5-6). At age 7 years, the overall prevalence of current productive cough was 47·0%
180 and similar across each subclass (Figure 3A). It reduced to 9·7% at age 13 years. From age 13 years
181 onward, the prevalence of current productive cough was highest for the "chronic productive cough",
182 followed by "intermittent productive" and "cough with allergies"; all of which were significantly
183 higher than "minimal cough" over time. The prevalence of current productive cough in the "cough
184 with colds only" was only slightly higher than "minimal cough" from age 7 to age 43 years; but there
185 was a dramatic increase at age 53 years (Figure 3A; Table S4, supplements pp 5). The "chronic
186 productive cough" had the highest prevalence of ever chronic productive cough at all times, followed
187 by the "intermittent productive" and "chronic dry" cough subclasses (Figure 3B; Table S4
188 supplements pp 5).

189 We investigated the distributions of previously published longitudinal lung function trajectories for
190 FEV_1, FVC, and FEV_1/FVC (data collected at six time-points at ages 7, 13, 18, 45, 50, and 53 years,
191 Appendix 1, supplements pp 11),[20,24] within each current adult cough subclass (Figure 4; Table S5,
192 supplements pp 6). Compared to "minimal cough", the two productive cough subclasses ("chronic
193 productive" and "intermittent productive") had worse FEV_1 and FEV_1/FVC trajectories. The "early
194 below average, accelerated decline" FEV_1 trajectory was only present in 1·5% of participants
195 belonging to "minimal cough", while the proportions were 14·2% and 9·7% for the two productive
196 cough subclasses. In contrast, "good" trajectories with high lung function and catch-up features were
197 less common in the two productive cough subclasses. For example, the "early low accelerated
198 growth, normal decline" FEV_1 trajectory made up 8·5% of the "minimal cough", but only 1·1% of
199 the "chronic productive cough". While such proportions for the "early high-normal decline"
200 FEV_1/FVC trajectory were 19·1% for "minimal cough" and 8·7% for "chronic productive cough"
201 (Table S5, supplements pp 6).

202 Similar patterns were seen for lifetime prevalence of asthma and allergy. Compared to "minimal
203 cough", the prevalence of current asthma from age 7 to 53 years was higher for participants
204 belonging to all other cough subclasses, but the difference was minimal for those belonging to
205 "cough with colds only" (Table S4, supplements pp 5; Figure S2 supplements pp 15). Longitudinal
206 trajectories for asthma and allergies were also distributed differently across cough subclasses.
207 Participants belonging to the "cough with allergies" had the highest proportion of late-onset asthma,

hay fever and allergies trajectories; and those belonging to the "chronic productive cough" had the highest proportion of early-onset asthma and allergies trajectories (Table S6, supplements pp 6; Figure S3, supplements pp 15).

As for smoking, the prevalence of smoking and second-hand smoking (SHS) decreased over time in the study population. However, the "chronic productive cough" had the highest prevalence of active smoking during middle age while both "chronic productive" and "intermittent productive" cough subclasses had the highest prevalence of SHS at all times (Figure S4; Table S4, supplements pp16-19).

In our sensitivity analysis, we compared cough subclasses to standard definitions of chronic cough (CC, cough > three months, with or without phlegm) and chronic bronchitis (CB, cough with phlegm >three months in two consecutive years). The clinical features of participants with standard CB were essentially the same as those with our "chronic productive cough" subclass. The clinical features of participants with standard CC sat in between "chronic dry cough" and "chronic productive cough" cough. This is expected as CB by definition was a subset of CC (Tables S8-10, supplements pp 8-10 Figure S5, supplements pp 17-19).

As for "non-coughers", they were mostly comparable to the "minimal cough", except non-coughers had lower smoking rates at all times. Consequently, in comparison with other adult cough subclasses, we observed similar findings for both "minimal cough" and "non-coughers" (Tables S4-S7, supplements pp 5-7).

DISCUSSION

Within a long-term prospective population-based cohort study, we observed that 10% of middle-aged participants had "standard" chronic cough (cough > 3 months) while 61% of them reported some degree of cough, including colds that travelled to the chest. Using a data-driven technique, we identified six distinct cough subclasses, based on classic cough-related symptoms at age 53 years, the peak age of cough presentations to healthcare providers.[3] Furthermore, we related these six subclasses to comorbidities at the same age, as well as longitudinal asthma and allergy histories, smoking exposures, lung function trajectories, and cough symptoms since childhood. The two most clinically important subclasses were "chronic productive" and "intermittent productive" cough as

they are associated with the worst lifetime lung function trajectories. Participants belonging to these productive cough subclasses had increased lifetime prevalence of productive cough, asthma, and allergies from as early as seven years of age, compared with the "minimal cough" (reference group), highlighting the early life origins of adult cough. This contrasts with participants belonging to the "chronic dry cough" and "cough with allergies", whose symptoms and worsening of lung function commenced later in life (from mid-forties), and the "cough with colds only", who had reduced lung function (lower FEV_1/FVC ratios) and higher prevalence of asthma and cough only by the mid-fifties. We suggest that future studies may explore the roles of early-life factors (asthma and allergies, productive cough, and active/passive smoking) as potential longitudinal treatable traits for primary prevention of future cough.

Only two studies have previously investigated cough phenotypes/subclasses in general populations,[9,16] but neither had comprehensive longitudinal data, especially over six decades. One study manually classified cough phenotypes among people with chronic cough, from their underlying diagnoses (i.e., asthma, GORD, smoking, etc.).[9] We used LCA, a more complex and holistic approach to objectively classify symptom profiles. The other study also used a data-driven method, K-means cluster analysis, to identify cough clusters among coughers,[16] but did not have data to link these clusters to longitudinal clinical characteristics.

"Chronic productive cough" was the most clinically impactful subclass in our study. It was associated with the highest prevalence of comorbidities including COPD, asthma, CRS, obstructive sleep apnea (OSA), anxiety, and depression; and the worst spirometry measurements at age 53 years. It was also associated with the worst FEV_1 and FEV_1/FVC trajectories: those with persistently low and/or rapid declines from childhood to mid-fifties. This subclass had the highest prevalence of asthma since age seven and the highest prevalence of productive cough since age 13 years. By definition, "chronic productive cough" resembled the standard definition of chronic bronchitis (CB), and we have shown that they had similar clinical characteristics. CB is a bronchial condition featuring mucus hypersecretion that is often caused by smoking.[25] Accordingly, we found that those belonging to the "chronic productive cough" subclass had the highest exposure to active and passive smoking at all ages (Figure S4, supplements pp16). These findings suggested that both smoking and early-life airway diseases (e.g., asthma) may contribute to the impaired lung function in the "chronic productive cough", and potentially to the development of COPD in later life. However, further analysis would be required to draw conclusions here and is beyond the scope of the current study.

Compared to the "chronic productive cough", participants belonging to the "intermittent productive cough" subclass had less exposure to active smoking, and shorter duration of cough, but otherwise similar risk profiles. These included low and rapid-decline FEV_1 and FEV_1/FVC trajectories, a high prevalence of asthma since childhood, and multiple comorbidities in middle age. This subclass was also associated with productive cough from an early age. These similarities between chronic and intermittent productive cough subclasses suggest a distinct pathophysiological airway mechanism, potentially involving airway chronic infection, inflammation, epithelial activation and wall remodelling, leading to subsequent progressive airflow narrowing and ultimately COPD.[26] Chronic productive cough (and/or CB), has been linked to the development of COPD, and future mortality, independent of smoking and lung function.[27] Our findings have added further evidence that intermittent productive cough may also be a risk factor for such adverse outcomes. These findings suggest that routine spirometry should be considered when managing productive cough.

In contrast, for the "chronic dry cough" and "cough with allergies", associated risks were less and presented at a later age (i.e., productive cough at age 43, lung function decline at 53 years) and to a lesser extent. Participants belonging to the "chronic dry cough" had better lung function than the productive cough subclasses, but the prevalence of comorbidities at age 53 years including GORD, anxiety, and depression was still high. The "cough with allergies" was associated with a higher prevalence of asthma and allergies since early life. This potentially led to the low lifetime smoking exposure due to avoidance, as well as the declined FEV_1/FVC ratios. This "cough with allergies" may be related to eosinophilic airway inflammation or cough hypersensitivity, as a previous study has found links between persistent cough in the pollen season and serum specific levels.[28] Future studies should explore the potential of allergy/serum IgE as a treatable trait of such cough, by assessing treatment responsiveness to nasal and/or inhaled corticosteroids. The "cough with colds only" subclass may represent a predominantly post-infective cough, suggested by the high prevalence of recent respiratory infections and similar clinical characteristics to "minimal cough".

Our study substantially advanced the current understanding of the heterogeneity of cough symptoms, especially among general populations. Our symptom-based framework is informative and easy to apply in primary healthcare settings but its relevance should be investigated for patients referred to cough clinics and/or recruited to clinical trials.[1,5] For instance, we found that the presence of phlegm is a distinguishing feature between adult cough subclasses. However, the importance of phlegm is currently only mentioned in the paediatric cough guidelines,[28,29] not the adult cough guidelines.[3,6]

Current adult guidelines recommend phenotyping firstly by cough duration and then by aetiology (underlying diagnoses).[3,6] This is because earlier studies recruiting cough patients from tertiary hospitals found that the duration of cough was a reliable predictor of the underlying diagnoses, while other features (phlegm, timing, and sound of the cough) were not.[7,8] While our findings may not be applicable to the highly-selected patients seen in specialised cough clinics, there are important implications at least for primary/secondary healthcare providers and further research in that context. Our data suggest that productive cough, even with a short duration, could be a marker of potentially worsening lung function and other comorbidities. Therefore, routine lung function tests in the diagnostic work-up of patients with productive cough are warranted, regardless of their smoking status and/or persistence of cough, with consideration for further investigations and/or specialist referrals from the treating primary care clinician. This is especially important considering that cough is mostly managed in primary care settings, where there is limited access to tests such as fractional concentration of exhaled nitric oxide (FeNO) or CT scans.[30] Furthermore, our data also suggested that performing spirometry on patients with a productive cough in primary care could help identify patients with COPD at an early stage.

Future studies should also consider measuring and analysing the co-presence of phlegm with cough, which is not reflected by the current definitions of cough hypersensitivity and/or refractory chronic cough. Studies in clinical settings with complete data on lung function and the presence of phlegm (dry or productive cough) are needed to further inform the management of dry/productive cough in specialized cough clinics.

To the best of our knowledge, this is the first study to describe the longitudinal history of cough especially in relation to other clinical characteristics, from childhood to mid-fifties in a general population. Our study was unique for several reasons: firstly, we used cough data at age 53 years, an age when the prevalence of chronic cough is known to peak.[3] Secondly, we applied LCA, a data-driven method, which allowed us to group cough-related symptoms into a specific subclass as participants often had more than one cough-related symptom. Thirdly, it was longitudinal with comprehensive data collected from age 7 to 53 years, so we could relate our cough subclasses to life course lung function trajectories.

There are some limitations. We did not have specific details on cough severity, measurements of cough hypersensitivity, healthcare utilisation or quality of life as measured by validated questionnaires. This is mainly because these definitions and questionnaires were developed for

clinical settings in recent times,[3,5] when our longitudinal study was already set up. We also used three months to define chronic cough as asked in the historical respiratory questionnaire, rather than the current eight-weeks definition. But the questionnaire we used has been validated, and been widely used in other epidemiological studies.[31,32] Data on ACE inhibitor use, GORD, and CRS were only collected once at age 53 years. "Current productive cough" was defined differently in childhood and adulthood, but the agreement between different definitions was high. Attrition was also inevitable as participants were followed over six decades. Not all statistics (i.e., BICs of the 3-class and 6-class models) may support our final LCA model as the optimal model, but this model has acceptable values for all statistics and more importantly, a plausible clinical interpretation (see Appendix-2 in supplement pp13-14). Inevitably, we may not have controlled for all known and unknown confounders as this is an exploratory analysis modelled for associations, not causation. The TAHS population is almost exclusively Caucasian and was born and mostly living in the State of Tasmania, so the findings should be generalised to other ethnicities and geographic locations with caution, and ideally validated in such cohorts when they become available.

In conclusion, we have described the heterogeneity of real-world cough by identifying six novel adult cough subclasses in a general middle-aged population. Each subclass had distinct clinical and spirometric characteristics over six decades. In the community and/or primary health care, our evidence indicates that productive cough should be managed proactively including by routine/regular measurement of lung function. Our study also highlights potential opportunities for early prevention and screening of other chronic airway diseases, such as asthma and COPD, through the early identification of high-risk cough subclasses. These LCA-defined cough subclasses are a substantial refinement of the current epidemiological definition of chronic cough, addressing the heterogeneity and complexity of cough. This framework could be applied to the management of cough in the community and to guide future therapeutic studies to understand varying treatment responses. It may also be expanded by adding risk factors, comorbidities, and demographic features once their associations are established to map out the heterogeneity of cough beyond symptoms. Future studies, including clinical trials, should measure features of cough (i.e., dry or productive cough) at baseline and take them into account in the analysis. Investigations into potential treatable traits of different cough subclasses are also indicated for future research, including early-life factors (airway conditions and active/passive smoking) and asthma/allergies.

AUTHOR'S CONTRIBUTIONS

Study concept and design: SCD, EHW, ABC, CJL, JLP, JZ; Acquisition of data: SCD, EHW, GSH, PST, MJA, ALJ, BE; Analysis and interpretation of data: JZ, DSB, SCD, JLP, CJL, ABC, EHW, CVS, AJL; Statistical analysis: JZ, DSB, CJL, SCD, JLP; Drafting of the manuscript: JZ, ABC, EHW, SCD, JLP, CJL; Supervision: SCD, JLP, CJL; Critical revision of the manuscript for important intellectual content: all authors; Decisions to submit the manuscript: all authors; Obtained funding: SCD, EHW, GSH, PST, MJA; JZ and SCD had directly accessed and verified the underlying data reported in the manuscript.

CONFLICTS OF INTEREST

SCD, CJL, AJL, DSB, MJA and JLP hold investigator-initiated grants from GlaxoSmithKline for unrelated research. SCD, AJL, and MJA hold investigator-initiated grants from Sanofi for unrelated research. AJL received non-financial support from Primus Pharmaceuticals for unrelated research. ABC hold investigator-initiated grants from NHMRC and Australian Medical Research Future Fund for unrelated research. JLP and SCD hold an investigator-initiated grant from AstraZeneca for unrelated research, received personal payment for Up-To-Date for chapters on cough and bronchiectasis, and payment to institutions for BMJ evidence for asthma. ABC also is a member of DSMB for unlicensed vaccines, and had roles in NHMRC Health Impact Committee, NHMRC Women in Science and ERS Guideline Committee without payments. MJA hold investigator-initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research, has undertaken an unrelated consultancy for Sanofi and received a speaker's fee from GSK, and is an honorary member of Independent Data Monitoring committee for NHMRC funded VCAPS4 trial through Woolcock Institute. All other authors declare no competing interests.

DATA SHARING

Individual participant data can be provided on request to anyone with a suitable proposal. The proposal will be considered by the Tasmanian Longitudinal Health Study (TAHS) steering committee, Requests can be directed to SCD (who is the principal investigator of TAHS and the corresponding author of this paper). Data for all TAHS participants can be provided.

ACKNOWLEDGEMENTS

We acknowledge the TAHS study participants and previous investigators. We also acknowledge all the respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland, Western Australia and New South Wales; the research interviewers, data entry operators and research officers. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 TAHS questionnaire. TAHS was supported by the National Health and Medical Research Council (NHMRC) of Australia under NHMRC project grant schemes (299901, 1021275); The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland & Tasmanian Asthma Foundations; The Royal Hobart Hospital; the Helen MacPherson Smith Trust; and GlaxoSmithKline. SCD, JLP, CJL, DSB and ABC are supported by the NHMRC of Australia. JLP is supported by Asthma Foundation, Craig Clifford Medical Trust, Helen McPherson Trust, and GlaxoSmithKline. JZ is supported by the University of Melbourne and the China scholarship council (CSC) joint PhD scholarship.

References

1. Mazzone SB, Chung KF, McGarvey L. The heterogeneity of chronic cough: a case for endotypes of cough hypersensitivity. *The Lancet Respiratory medicine* 2018; **6**(8): 636-46.
2. Chung KF, Pavord ID. Prevalence, pathogenesis, and causes of chronic cough. *The Lancet* 2008; **371**(9621): 1364-74.
3. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *European Respiratory Journal* 2020; **55**(1).
4. Feng W, Zhang Z, Liu Y, et al. Association of chronic respiratory symptoms with incident cardiovascular disease and all-cause mortality: findings from the Coronary Artery Risk Development in Young Adults Study. *Chest* 2021. Apr 1;**161**(4):1036-45.
5. Chung KF, McGarvey L, Song WJ, et al. Cough hypersensitivity and chronic cough. *Nature reviews Disease primers* 2022; **8**(1): 45.
6. Irwin RS, French CL, Chang AB, et al. Classification of cough as a symptom in adults and management algorithms: CHEST guideline and expert panel report. *CHEST* 2018; **153**(1): 196-209.
7. Mello CJ, Irwin RS, Curley FJ. Predictive Values of the Character, Timing, and Complications of Chronic Cough in Diagnosing Its Cause. *Archives of Internal Medicine* 1996; **156**(9): 997-1003.
8. Smyrnios NA, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest* 1995; **108**(4): 991-7.
9. Abozid H, Baxter CA, Hartl S, et al. Distribution of chronic cough phenotypes in the general population: A cross-sectional analysis of the LEAD cohort in Austria. *Respir Med* 2021; **192**: 106726.
10. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *The European respiratory journal* 2016; **47**(2): 410-9.
11. Sadeghi MH, Wright CE, Hart S, Crooks M, Morice A. Phenotyping patients with chronic cough: Evaluating the ability to predict the response to anti-inflammatory therapy. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2018; **120**(3): 285-91.

12. Kang J, Moon JY, Kim DK, Kim JW, Jang SH, Koo HK. Cough Characteristics and Their Association Patterns According to Cough Etiology: A Network Analysis. *Journal of clinical medicine 2023*; **12**(16).
13. Kang J, Seo WJ, Kang J, et al. Clinical phenotypes of chronic cough categorised by cluster analysis. *PloS one* 2023; **18**(3): e0283352.
14. Irwin RS, Boulet L-P, Cloutier MM, et al. Managing Cough as a Defense Mechanism and as a Symptom: A Consensus Panel Report of the American College of Chest Physicians. *Chest* 1998; **114**(2, Supplement): 133S-81S.
15. Kaulamo JT, Lätti AM, Koskela HO. Healthcare-Seeking Behaviour Due to Cough in Finnish Elderly: Too Much and Too Little. *Lung* 2023: 1-10.
16. Koskela HO, Selander TA, Lätti AM. Cluster analysis in 975 patients with current cough identifies a phenotype with several cough triggers, many background disorders, and low quality of life. *Respir Res* 2020; **21**(1): 1-9.
17. Matheson MC, Abramson MJ, Allen K, et al. Cohort profile: the Tasmanian longitudinal health study (TAHS). *Int J Epidemiol* 2017; **46**(2): 407-8i.
18. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *The European respiratory journal* 2005; **26**(2): 319-38.
19. Hall GL, Thompson BR, Stanojevic S, et al. The Global Lung Initiative 2012 reference values reflect contemporary Australasian spirometry. *Respirology (Carlton, Vic)* 2012; **17**(7): 1150-1.
20. Dharmage SC, Bui DS, Walters EH, et al. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *The Lancet Respiratory medicine* 2022. Mar 1;11(3):273-82.21. Weller BE, Bowen NK, Faubert SJ. Latent Class Analysis: A Guide to Best Practice. *Journal of Black Psychology* 2020; **46**(4): 287-311.
22. Bui DS, Lodge CJ, Perret JL, et al. Trajectories of asthma and allergies from 7 years to 53 years and associations with lung function and extrapulmonary comorbidity profiles: a prospective cohort study. *The Lancet Respiratory medicine* 2021; **9**(4): 387-96.
23. Lanza ST, Dziak JJ, Huang L, Wagner AT, Collins LM, University Park: The Methodology Center, Penn State. LCA Stata plugin users' guide (Version 1.2). 2015. Available from methodology.psu.edu.
24. Bui DS, Agusti A, Walters H, et al. Lung function trajectory and biomarkers in the Tasmanian Longitudinal Health Study. *ERJ Open Res* 2021; **7**(3).

461 25. Oswald NC, Medvei VC. Chronic bronchitis; the effect of cigarette-smoking. *Lancet*
462 *(London, England)* 1955; **269**(6895): 843-4.
463 26. Hughes R, Rapsomaniki E, Janson C, et al. Frequent productive cough: Symptom burden and
464 future exacerbation risk among patients with asthma and/or COPD in the NOVELTY study. Respir
465 Med 2022; 200: 106921.
466 27. Satia I, Mayhew AJ, Sohel N, et al. Impact of productive and dry chronic cough on mortality
467 in the Canadian Longitudinal Study on Aging (CLSA). *J Thorac Dis* 2022; **14**(12): 5087-96.
468 28. Matsumoto H, Izuhara Y, Niimi A, et al. Risks and cough-aggravating factors in prolonged
469 cough epidemiological observations from the Nagahama Cohort Study. Annals of the American
470 Thoracic Society 2017; 14(5): 698-705.
471 29. Chang AB, Oppenheimer JJ, Irwin RS, et al. Managing chronic cough as a symptom in
472 children and management algorithms: chest guideline and expert panel report. *CHEST* 2020; **158**(1):
473 303-29.
474 30. Ringus DL, Li SH, Vu TT, et al. Management and referral patterns for new-onset chronic
475 cough in primary care patients. *Allergy and asthma proceedings* 2022; **43**(6): e72-e9.
476 31. Burney P, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health
477 Survey. *European Respiratory Journal* 1994; **7**: 954-60.
478 32. Flexeder C, Zock JP, Jarvis D, et al. Second-hand smoke exposure in adulthood and lower
479 respiratory health during 20 year follow up in the European Community Respiratory Health Survey.
480 *Respir Res* 2019; **20**(1): 3

Table 1 Demographic and clinical characteristics of participants across the six cough subclasses at age 53 years identified by latent class analysis.

Cough subclasses	1. Minimal cough (reference)	2. Cough with colds only	3. Cough with allergies	4. Intermittent productive cough	5. Chronic dry cough	6. Chronic productive cough
N (%)	206 (9.3%)	1189 (53.7%)	305 (13.8%)	213 (9.6%)	147 (6.6%)	153 (6.9%)
Australian-born ‡	200 (97.1%)	1147 (96.5%) 0.90	291 (95.4%) 0.34	205 (96.2%) 0.63	141 (95.9%) 0.48	148 (96.7%) 0.85
Female	105 (51.0%)	596 (50.1%) 0.82	204 (66.9%) <0.001	93 (43.7%) 0.13	76 (51.7%) 0.89	74 (48.4%) 0.63
Education		0.43	0.42	0.021	0.64	0.19
< 12 years	69 (34.0%)	375 (31.8%)	88 (29.1%)	93 (44.3%)	46 (31.9%)	66 (43.4%)
=12 years	92 (45.3%)	511 (43.3%)	140 (46.4%)	92 (43.8%)	62 (43.1%)	60 (39.5%)
≥University	42 (20.7%)	294 (24.9%)	74 (24.5%)	25 (11.9%)	36 (25.0%)	26 (17.1%)
Smoking		0.063	<0.001	0.61	0.53	<0.001
Never	79 (38.9%)	480 (40.9%)	149 (49.3%)	75 (35.4%)	59 (41.0%)	39 (26.2%)
Past	72 (35.5%)	476 (40.5%)	118 (39.1%)	74 (34.9%)	43 (29.9%)	35 (23.5%)
Current	52 (25.6%)	219 (18.6%)	35 (11.6%)	63 (29.7%)	42 (29.2%)	75 (50.3%)
SHS exposure	36 (17.7%)	238 (20.3%) 0.41	42 (13.9%) 0.24	65 (31.7%) 0.001	33 (22.6%) 0.26	47 (31.3%) 0.003
BMI (kg/m^2)	27.8 (5.1)	28.7 (5.4) 0.019	29.3 (6.3) 0.004§	29.8 (6.3) <0.001	29.5 (5.7) 0.005§	28.8 (6.3%) 0.12§
Obesity	64 (31.5%)	395 (33.6%) 0.57	115 (37.8%) 0.15	83 (39.7%) 0.083	53 (37.1%) 0.28	54 (35.8%) 0.40
Pneumonia	29 (14.1%)	255 (21.6%) 0.014	78 (25.9%) 0.001	53 (24.9%) 0.005	33 (22.5%) 0.042	37 (24.2%) 0.015
GORD	18 (8.8%)	148 (12.5%) 0.12	48 (15.8%) 0.020	31 (14.6%) 0.063	23 (15.9%) 0.042	23 (15.0%) 0.064
Current COPD	5 (3.4%)	56 (6.5%) 0.15	22 (8.5%) 0.050	23 (15.2%) <0.001	13 (11.6%) 0.011	28 (26.9%) <0.001
Current CRS	8 (3.9%)	60 (5.1%) 0.477	38 (12.5%), 0.001	28 (13.2%) 0.001	16 (10.9%) 0.010	24 (15.8%) <0.001
Current asthma	31 (15.1%)	298 (25.1%) 0.002	134 (43.9%) <0.001	113 (53.3%) <0.001	72 (49.0%) <0.001	97 (63.4%) <0.001
Respiratory infection in the last 3 wks	5 (3.2%)	100 (11.1%) 0.003	21 (7.9%) 0.055	10 (6.4%) 0.19	7 (5.9%) 0.28	10 (9.1%) 0.042
ACE inhibitor use in the last 72 hrs	17 (11.2%)	76 (8.6%) 0.30	29 (11.0%) 0.95	21 (13.6%) 0.53	16 (13.8%) 0.52	10 (9.2%) 0.60
Current hay fever	74 (35.9%)	431 (36.3%) 0.91	220 (72.1%) <0.001	101 (47.4%) 0.017	81 (55.1%) <0.001	90 (58.8%) <0.001
Current eczema	10 (4.9%)	98 (8.3%), 0.093	32 (10.5%), 0.024	26 (12.3%), 0.007	22 (15.1%), 0.001	17 (11.1%), 0.027
Current food allergy	15 (7.4%)	152 (12.9%), 0.025	74 (24.5%), <0.001	26 (12.4%), 0.084	28 (19.4%), 0.001	24 (16.0%), 0.010
OSA Berlin risk	58 (30.7%)	433 (38.6%) 0.038	110 (39.0%) 0.065	96 (48.2%) <0.001	70 (51.1%) <0.001	74 (54.4%) <0.001
OSA STOP-Bang		0.031	0.035	0.010	0.059	0.023
Low risk	67 (42.7%)	302 (33.0%)	103 (40.6%)	48 (28.1%)	36 (29.0%)	29 (26.4%)
Moderate risk	42 (26.8%)	329 (36.0%)	96 (37.8%)	47 (27.5%)	39 (31.5%)	36 (32.7%)
High risk	48 (30.6%)	283 (31.0%)	55 (21.7%)	76 (44.4%)	49 (39.5%)	45 (40.9%)
Current anxiety (GAD≥10)	11 (5.5%)	113 (9.7%) 0.058	32 (10.7%) 0.043	36 (17.1%) <0.001	23 (15.7%) 0.002	31 (20.7%) <0.001
Current depression (PHQ≥10)	13 (6.6%)	86 (7.4%) 0.71	25 (8.5%) 0.46	28 (13.8%) 0.019	18 (12.3%) 0.070	23 (13.9%) 0.006

Data are shown as n (%), n/N (%), or mean (SD), P values. P values compared with the "Minimal cough" subclass using Chi-Square tests or independent t-tests.
§ Welch's test with the Satterthwaite approximation was taken due to unequal variance.
ǂ Country of birth: Australia / other countries. Detailed definitions of each variable were shown in Table S2 (supplements, pp3).
Abbreviations: ACE: angiotensin-converting enzyme. BMI: body mass index; COPD: chronic obstructive pulmonary disease, defined as post-bronchodilator $FEV_1/FVC < 0.7$, CRS: chronic rhinosinusitis, GAD-7, 7-item anxiety scale for generalised anxiety disorder, GORD: Gastro-oesophageal Reflux disease, OSA: obstructive sleep apnea, PHQ-9: the patient health questionnaire, depression model; SHS: second-hand smoking, STOP-Bang: snoring, tiredness, observed apnea, high blood pressure, BMI, age, neck circumference and male sex questionnaire.
Missing data (n): ACE inhibitor (530), education (22), smoking (33), BMI (26), COPD (574), respiratory infection (504), asthma (7), GORD (13), pneumonia (11), current asthma (2), CRS (6), current eczema (9), current anxiety (44), current depression (61), food allergy (26), hay fever (3), OSA risks (148).