Author/s:
Campbell, B;Simpson, JA;Bui, DS;Lodge, CJ;Lowe, AJ;Matheson, MC;Bowatte, G;Burgess, JA;Hamilton, GS;Leynaert, B;Gómez Real, F;Thomas, PS;Giles, GG;Frith, PA;Johns, DP;Mishra, G;Garcia-Aymerich, J;Jarvis, D;Abramson, MJ;Walters, EH;Perret, JL;Dharmage, SC

Title:
Early menarche is associated with lower adult lung function: A longitudinal cohort study from the first to sixth decade of life

Date:
2020-03-01

Citation:
Campbell, B., Simpson, J. A., Bui, D. S., Lodge, C. J., Lowe, A. J., Matheson, M. C., Bowatte, G., Burgess, J. A., Hamilton, G. S., Leynaert, B., Gómez Real, F., Thomas, P. S., Giles, G. G., Frith, P. A., Johns, D. P., Mishra, G., Garcia-Aymerich, J., Jarvis, D., Abramson, M. J. ,... Dharmage, S. C. (2020). Early menarche is associated with lower adult lung function: A longitudinal cohort study from the first to sixth decade of life. Respirology, 25 (3), pp.289-297. https://doi.org/10.1111/resp.13643.

Campbell Brittany (Orcid ID: 0000-0002-0041-5543)
Hamilton Garun (Orcid ID: 0000-0002-1744-2839)
Frith Peter (Orcid ID: 0000-0003-3265-0131)
Johns David (Orcid ID: 0000-0002-1575-6850)
Garcia Aymerich Judith (Orcid ID: 0000-0002-7097-4586)
Abramson Michael (Orcid ID: 0000-0002-9954-0538)
Perret Jennifer (Orcid ID: 0000-0001-7034-0615)
Dharmage Shyamali (Orcid ID: 0000-0001-6063-1937)

Editorial Office Notes:

RES-18-615.R2

ORIGINAL ARTICLE

Received 4 Septemver 2018
Invited to revise 16 November 2018 and 29 March 2019
Revised 30 January and 27 April 2019
Accepted 29 May 2019
Associate Editor: Stacey Peterson-Carmichael
Senior Editor: Fanny Ko

Publication fee waiver: NO
Volume: 24

Early menarche is associated with lower adult lung function: A longitudinal cohort study from the 1st to 6th decade of life

Brittany Campbell[1], MSc, Julie A. Simpson[2], PhD, Dinh S. Bui[1], MPH, Caroline J. Lodge[1], PhD, Adrian J. Lowe[1], PhD, Melanie C. Matheson[1], PhD, Gayan Bowatte[1], PhD, John A. Burgess[1], PhD, Garun S. Hamilton[3,4,5], PhD, Benedicte Leynaert[6], PhD, Francisco Gómez Real[7,8], PhD, Paul S. Thomas [9],MD, Graham G. Giles[1,10], PhD, Peter A. Frith[11,12], PhD, David P. Johns[13], PhD, Gita Mishra[14], PhD, Judith Garcia-Aymerich[15,16,17], PhD, Debbie Jarvis[18], MD, Michael J. Abramson[19], PhD, E. Haydn Walters[1], DM, Jennifer L. Perret[1,20], PhD, Shyamali C. Dharmage[1], PhD

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

[2]*Biostatistics Unit, Centre for Epidemiology & Biostatistics, Melbourne School of Population & Global Health, The University of Melbourne, VIC, Australia*

[3] *Monash Lung and Sleep, Monash Health, VIC, Australia*

[4] *School of Clinical Sciences, Monash University, VIC, Australia*

[5] *Monash Partners – Epworth, VIC, Australia*

[6] *Inserm U1152, Pathophysiology and Epidemiology of Respiratory Diseases, F-75890, Paris, France, University Paris Diderot Paris 7, UMR 1152, F-75890, Paris, France*

[7] *Haukeland University Hospital, Bergen, Norway*

[8] *Department of Clinical Science, University of Bergen, Bergen, Norway*

[9]*Faculty of Medicine, University of New South Wales, NSW, Australia*

[10]*Cancer Epidemiology and Intelligence Division, Cancer Council Victoria, Melbourne, VIC, Australia*

[11]*Southern Adelaide Local Health Network, SA, Australia*

[12]*School of Health Sciences, The University of South Australia, SA, Australia*

[13]*Breathe Well: Centre of Research Excellence for Chronic Respiratory Disease and Lung Ageing, School of Medicine, University of Tasmania*

[14]*School of Public Health, The University of Queensland, Brisbane, QLD, Australia*

[15]*ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain*

[16]*Universitat Pompeu Fabra (UPF), Barcelona, Spain*
[17]*CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain*

[18]*National Heart and Lung Institute, Imperial College, London, UK*

[19]*School of Public Health & Preventive Medicine, Monash University, VIC, Australia*
[20]*The Institute for Breathing and Sleep (IBAS), Heidelberg, VIC, Australia*

Correspondence:
Prof. Shyamali Dharmage 207 Bouverie St, Carlton, VIC AUS 3053;
s.dharmage@unimelb.edu.au

SUMMARY AT A GLANCE: This is the first longitudinal study with data on key early life confounders to link early age at menarche to lung function deficits in middle-age and provide novel evidence on potential biological pathways contributing to this link.

Author contribution roles using the CRediT Taxonomy

Please complete this Table on behalf of and with approval of all authors

-Note that not all categories are relevant to each type of research → Only select those contribution roles that are relevant to your study.

-This information will be translated into an '*Author contribution statement*' by the typesetters and included at the end of your publication → The corresponding author is responsible for checking the *'Author contribution statement'* against the completed table below in the final version of the manuscript.

- DO NOT FORGET: If not done yet, you will ALSO be required to complete the same **Author contribution information for all authors in ScholarOne at Step 4 of the First Look** finalization.

Role	***Degree***	***Author initials*** *(reflecting the full author name on the manuscript)*
1 **-Conceptualization**	Lead	SCD
	Equal	EHW, MJA
	Supporting	CJL, AJL, MCM, GB, JAB, GSH, PST, GGG, PAF, DPJ, JLP
2 **- Data curation**	Lead	SCD
	Equal	BC
	Supporting	DSB,CJL, AJL, MCM, GB, JAB, GSH, PST, GGG, PAF, DPJ, JLP, EHW, MJA
3 **-Formal analysis**	Lead	BC
	Equal	
	Supporting	JAS
4 **- Funding acquisition**	Lead	SCD
	Equal	
	Supporting	MCM, CJL, AJL, MCM, GB, JAB, GSH, PST, GGG, PAF, DPJ, JLP, EHW, MJA
5 **- Investigation**	Lead	SCD
	Equal	EHW, MJA
	Supporting	
6 **- Methodology**	Lead	SCD
	Equal	BC
	Supporting	
7 **- Project administration**	Lead	SCD
	Equal	
	Supporting	
8 **- Resources**	Lead	SCD
	Equal	
	Supporting	MCM, CJL, AJL, MCM, GB, JAB, GSH,PST, GGG, PAF, DPJ, JLP, EHW, MJA
9 **- Software**	Lead	N/A
	Equal	
	Supporting	
10 **- Supervision**	Lead	N/A

	Equal	
	Supporting	
11 - **Validation**	Lead	N/A
	Equal	
	Supporting	
12 - **Visualization**	Lead	N/A
	Equal	
	Supporting	
13 - **Writing – original draft**	Lead	BC
	Equal	
	Supporting	SCD, JAS, JLP
14 - **Writing – review & editing**	Lead	BC
	Equal	
	Supporting	DSB, JAS, MCM, CJL, AJL, MCM, GB, JAB, GSH, PST, GGG, PAF, DPJ, JLP, BL, FGR, GM, JGA, DJ, SCD

ABSTRACT

Background and objective: Early-menarche is increasing in prevalence worldwide, prompting clinical and public health interest on its links with pulmonary function. We aimed to investigate the relationship between early menarche and lung function in middle age.

Methods: The population-based Tasmanian Longitudinal Health Study (born 1961; n=8,583), was initiated in 1968. The 5th Decade follow-up data (mean age 45-years) included age-at-menarche and complex lung function testing. The 6th Decade follow-up (age 53-years) repeated spirometry and gas transfer factor. Multiple linear regression and mediation analyses were performed to determine the association between age-at-menarche and adult lung function and investigate biological pathways, including the proportion mediated by adult-attained height.

Results: Girls reporting an early-menarche (<12 years) were measured to be taller with greater lung function at age 7 years compared with those reporting menarche ≥12 years. By 45 years of age they were shorter and had lower post-bronchodilator forced expiratory volume in one second (adjusted mean difference -133mL; 95%Confidence Interval (CI) -233,-33), forced vital capacity (-183mL; 95%CI -300,-65), and functional residual capacity (-168mL; 95%CI -315,-21). Magnitudes of spirometric deficits were similar at age 53 years. Forty percent of these total effects were mediated through adult-attained height.

Conclusion: Early-menarche was associated with reduced adult lung function. This is the first study to investigate post-bronchodilator outcomes and quantify the partial role of adult height in this association.

Short title: Menarchal age and adult lung function

Keywords: Pulmonary Function Tests, Menarche, Epidemiology, Cohort Studies, Longitudinal Studies

INTRODUCTION

Secular trends have suggested a decreasing age at menarche and pubertal onset over recent decades.(1,2) It has been hypothesised that this trend is likely a consequence of various factors including changes in nutritional intake, living conditions, and reductions in childhood morbidity and mortality associated with infectious diseases.(3) However, early life stressors, increasing rates of prepubertal obesity, and exposure to endocrine-disrupting compounds may also play a role in driving earlier pubertal onset.(4)

Concerningly, early menarche, a notable marker of wider pubertal development, has been identified as a risk factor for a host of chronic diseases including breast and ovarian cancers, diabetes, cardiovascular disease, depression and increased all-cause mortality.(3,4) Additional evidence has also shown that females incur excess asthma-related morbidity and mortality from around the time of puberty, suggesting that pubertal changes in endogenous hormones or growth may have long-term consequences for respiratory health and disease susceptibility.(5–7) In light of this evidence, age at menarche has recently become a focus in research on determinants of respiratory health. Notably, a systematic review found early menarche to be associated with an increased risk of developing asthma, and other studies have reported associations with increased respiratory symptoms in adulthood.(8–10)

However, despite this evidence there are very few studies on the relationship between early menarche and objective measures of pulmonary function.

One study by Macsali et al, found that women who reached menarche at <11 years had lower pre-bronchodilator FEV_1 (-113 ml; 95%CI -196, -33) and FVC (-126 ml; 95% CI -223,-28) in adulthood, compared with those reaching menarche at the median age of 13 years.(11) A recent Mendelian randomisation study by Gill et al utilised age at menarche SNPs and found genetic proxies for menarchal age to be associated with short-term improvements in pre-bronchodilator adolescent lung function but impaired FVC in adulthood.(12) Yet this study found no associations with FEV_1 or FEV_1/FVC.

However, given this minimal evidence, significant gaps in our knowledge on these associations still exist. The relationships between early menarche and more comprehensive lung function measures has not been previously investigated. This includes serial post-bronchodilator spirometry, which has the potential to capture post-BD airflow limitation characteristic of chronic obstructive pulmonary disease and detect LF decline, along with lung volumes, gas transfer factor to assess lung function beyond the airways. Furthermore, no study has quantified the proportion of any indirect effects, via somatic growth (height/weight) or post-menarchal asthma, mediating the association between age at menarche and lung function. Long-term longitudinal studies with data on early life confounders are necessary to fill these critical knowledge gaps and investigate the close links between sexual development, somatic growth, and lung function.(13–16)

Considering the present research gaps and limited knowledge in this field, we hypothesised that an early age at menarche was associated with reduced pre- and post-bronchodilator lung function in middle age and that these relationships might be mediated through adult-attained height, weight, or asthma. Utilising longitudinal data from the Tasmanian Longitudinal Health Study (TAHS), we aimed to investigate these hypotheses by providing further evidence on the relationship between age at menarche and complex lung function, while also exploring the degree to which these associations were mediated through adult-attained height, weight, or asthma.

METHODS

Study population

Detailed methods of the population-based Tasmanian Longitudinal Health Study have been fully described previously.(17) Briefly, the baseline TAHS survey was conducted in 1968 and enrolled 8,583 Tasmanian children (born 1961), to investigate the prevalence and natural history of childhood asthma. At enrolment, parents completed a health questionnaire on behalf of their child, and each child participated in a clinical assessment including anthropometric measures and pre-bronchodilator spirometry.

The analyses performed here focused on participants (Figure 1) who reported the age at their first period during the 2002-2008 TAHS follow-up (termed 5th Decade follow-up) and subsequently participated in the 6th Decade follow-up (2012-2016). During the 5th Decade

follow-up, 3,510 female participants were traced (83.7% of females from the original cohort). Of those, 2,776 (66% percent of the original cohort) took part in the postal survey. Respondents who had participated in previous follow-ups and/or reported symptoms of asthma/cough were invited to participate in further clinical testing including the measurement of spirometry, static lung volumes, and diffusing capacity of the lungs for carbon monoxide ($T_L$co). During the 6th Decade follow-up, 2,965 female participants were invited to take part in the clinical study of whom 1,382 participated. Overall attrition and participant numbers for each TAHS follow-up have been published elsewhere.(17)

Data collection

FEV_1 , FVC and FEV_1/FVC ratio were measured in accordance with the joint American Thoracic Society and European Respiratory Society guidelines using the EasyOne Ultrasonic Spirometer [Ndd, Medizintechnik, AG, Switzerland].(18) Post-BD spirometry was obtained approximately 10 minutes after the administration of 300 μg of salbutamol.

During the 5th Decade follow-up, age at menarche was reported by 2,721 women. For these women, spirometry (n= 659), lung volumes (n=591), and T_{LCO} (n=608) were available from the 5th Decade follow-up in addition to repeated 6th Decade spirometry (n=1,235) and T_{LCO} (n=1,192) (Figure 1). A total of 412 women had spirometry measured at both the 5th and 6th Decades. In this analysis, primary outcome measures included continuous FEV_1, FVC, FEV_1/FVC, total lung capacity (TLC), residual volume (RV), RV/TLC, functional residual capacity (FRC), and diffusing capacity of the lung for carbon monoxide ($T_L$co). Rates of lung

function decline from the 5^{th}-6^{h} decades in FEV_1 and FVC (mL/year) were also calculated.

This study was approved by the Human Research Ethics Committees at The Universities of Melbourne (approval number 040375), Tasmania (040375.1), and New South Wales (08094), the Alfred Hospital (1118/ 04), and Royal Brisbane & Women's Hospital Health Service District (2006/037). Written informed consent was obtained from all participants.

Definitions

Exposure

During the 5^{th} Decade TAHS follow-up, female participants were asked "What was the age of your first period? (age in years)". Based on their response to this question women were categorised into an early menarche group (<12 years) or a later age menarche group (≥12 years).(8,11)

Confounders

A directed acyclic graph (DAG) was developed to illustrate hypothesised causal relationships between age at menarche, lung function and relevant covariates.(19) Parental smoking and pre-menarchal SES, asthma, and weight were identified as *a priori* confounders to be included for adjustment in all models for lung function analyses, as evidence suggests their potential to influence both pubertal age and lung function outcomes.(20–23)

Statistical Analysis

The distribution of baseline characteristics, body size measures, and smoking in early and late menarche groups were presented using mean (SD) or frequency (percent), as appropriate. Multiple linear regression was performed to estimate adjusted mean differences in lung function between early and late menarche groups. Effect modification of age at menarche and lung function associations by personal smoking and current asthma were investigated with 6th Decade outcomes, given larger participant numbers available. Mediation analyses were conducted to estimate the indirect effect of early menarche on adult lung function mediated through adult-attained height, weight, or current asthma.(24) As such, only absolute values of lung function (not height-adjusted transformations) were investigated. Sensitivity analyses were performed to test the robustness of mediation results through estimating the correlation in the error terms of the mediator and outcome models.(24) All analyses were performed with Stata 13 (StataCorp, College Station Texas).

RESULTS

Sample characteristics & age at menarche

Of the 2,721 participants who reported their age at menarche at the 5th Decade follow-up, 15.5% (423) reported reaching menarche before 12 years, and 84.5% (2,298) were ≥12 years.

When compared to females with menarche at or later than 12 years, those who reached menarche before 12 years were slightly taller at age seven years (121.2 cm vs 119.8 cm) and had minimally higher premenarchal lung function (FEV_1 1.31 L vs 1.29 L; FVC 1.44 L vs 1.39 L) (Table 1). A subsample (n=272) of these participants was also followed-up in 1974 (age 13) at which time girls with early menarche also had marginally better lung function (FEV_1 3.05L vs 2.86L; FVC 3.28 L vs 3.10L). As adults, women whose age at menarche was <12 years were shorter (162.4 cm vs 163.9 cm) and also had higher body mass indices (BMI) in both childhood and adulthood, compared with those who reported a later age at menarche.

A greater proportion of those reporting early menarche were current smokers at 45 and 53 years of age, and only small differences were observed in the proportions of parental smoking or family history of allergic disease between the early and later menarche groups.

Age at menarche & middle age lung function

Women with early menarche had lower pre and post-BD FEV_1 and FVC levels at a mean age of 45 and 53 years (Table 2). Compared with the reference group (age at menarche ≥12

years), women attaining menarche prior to 12 years of age had reduced post-BD FEV_1 and FVC of -133mL (95%CI -233, -33; p=0.009) and -183mL (95%CI -300, -65; p=0.002), respectively, at age 45. At 53 years of age, early menarche was associated with a similar reduction in post-BD FEV_1 (-171mL; 95%CI -236, -106; p<0.001) and FVC (-251mL; 95%CI -329, -174; p<0.001).

Early menarche was also associated with a statistically significant reduction in FRC (-168mL; 95%CI -315, -21; p=0.025). Although, reductions in RV (-100mL; 95%CI -216, 17 p=0.095) and TLC (-260mL; 95%CI -616, 97 p=0.15) did not reach statistical significance.

No interactions between age at menarche and potential effect modifiers, personal smoking and current asthma, were observed (p value for interaction >0.30). Although childhood lung function was not identified as a confounder based on the developed DAG, further adjustment for this did not materially change the presented estimates. Additionally, no difference in FEV_1/FVC ratio was observed between early and late menarche groups at the 5^{th} Decade follow-up, but a modest positive difference was observed in the 6^{th} Decade (Table 2).

There were no associations between early menarche and $T_L$co or lung function decline (mL/year) between the 5^{th} and 6^{th} Decade follow-ups (Supplement Table S1).

Association between age at menarche & lung function: mediation analyses

Mediation analyses were used to partition the direct and indirect effects (i.e. mediated through adult-attained height) of age at menarche on reduced FEV_1 and FVC at age 53 years and FRC at age 45 years (Table 3). An estimated 42% (-72mL; 95%CI -96, -47) of the total effect of early menarche on post-BD FEV_1, 40% of the total effect (-101mL; 95%CI -135, -67) for FVC, and 60% (-102mL; 95%CI -155, -51) for FRC were mediated through height. For pre-BD FEV_1 and FVC, a similar proportion of the total effect was mediated through height, leaving the majority of the association between age at menarche and adult lung function deficits unexplained by height. Minimal mediation on FEV_1 and FVC was observed through adult weight or asthma (all indirect effect estimates ≤7% of the total effect).

DISCUSSION

In this population-based cohort, women reporting an early age at menarche were taller and had greater lung function prior to menarche (measured at age 7 years), but had reduced FEV_1, FVC, FRC and height in mid-adult life as compared to women reporting a later age at menarche. Using mediation analyses, we were able to show, for the first time, that the observed association between early menarche and post-bronchodilator spirometry involved considerable mediation through lower adult-attained height (40%). However, the majority of the observed association was unexplained by adult height, weight or asthma, suggesting a predominant role of other mechanisms e.g. hormonal influences on pulmonary structure or inflammatory mediators, which have yet to be explored.(25) Also, we did not see associations

with lung diffusing capacity ($T_L$co) to suggest the presence of lung tissue involvement. Our findings on reduced FRC with early menarche are novel, although the magnitude of FRC reduction is modest and its clinical significance is not yet established.

The observed proportions of early (16%) and later (84%) age at menarche in this TAHS cohort are also consistent with findings from other studies estimating the proportion of girls menstruating by 11.1 years and experiencing early menarche (classified as <11.5 years) to be between 10% and 14.6%, respectively.(26,27) A recent publication highlighted the role of early life socioeconomic disadvantage in determining pubertal age. As this disadvantage may also contribute to lung function deficits, it is a potentially important confounder that we have been able to account for in our analyses.(28) Our models adjusted for other potential early life confounders: parental smoking, child's weight and current asthma at 7 years of age, whereas a previous study by Macsali et al, lacked such data on early life confounders.(11) Our new epidemiological findings, consistent with Macsali et al and the previous Mendelian randomisation observations on early menarche and impairments in FVC, strengthen existing evidence to support this relationship.(12)

Although our observations were largely consistent with Macsali's findings, we observed a greater effect size for FEV_1 and FVC. This difference is likely the result of adjustment for height in Macsali et al's multivariable models, which was excluded from our regression models.(11) This evidence raises a broader issue around the common practice of adjusting for height when using absolute lung function values and the use of height-adjusted z-score and

percent predicted outcome values. As in this case, when height is a mediator in the relationship between age of menarche (the exposure of interest) and lung function outcomes, it would be inappropriate to adjust for height or use transformations of lung function outcomes (e.g. z-score or %predicted) that inherently take differences in the attained height into account, as they would underestimate the association between the exposure and the outcome.

An accepted minimal clinically important difference (MCID) in relation to FEV_1 is currently debated. Although there is no clear consensus, explorations on the MCID in COPD suggests deficits as low as 100 mL may be perceived by patients, although the baseline lung function is relevant and greater deficits are likely to be clinically relevant for those with normal lung function.(29) Further consolidation of evidence, including literature reviewed by an American Thoracic Society/European Respiratory Society task force, has defined a range of 100 to 140 ml for a MCID and also suggested that regulators consider a 5 to 10% change in FEV_1 from baseline as clinically important, with less than 3% as not clinically important.(30,31) In this context, we acknowledge that the magnitude of some of our observed deficits, particularly at the lower range of our observed confidence limits, were modest and might only be symptomatically relevant for some individuals. The influence of early age at menarche on lung function deficits may be especially clinically relevant for susceptible individuals who have low baseline lung function and/or ongoing exposure to additional respiratory risk factors. Thus, these deficits associated with early menarche may

also predispose some women to increased vulnerability to further respiratory insults or accelerated lung function loss.

In other literature, age at menarche has been linked to subsequent general health and disease risk, and our data confirm that girls with earlier menarche reach a shorter adult height.(11,32–34) It has been postulated that increased oestrogen levels associated with the menarchal transition may play a role in driving earlier epiphyseal fusion.(32,35) Our findings suggest that differences in adult height only partly explain the relationship between early age at menarche and reduced spirometric adult lung function outcomes, while mediation through asthma or weight is minimal. Outside of this, it is possible that other crucial mechanisms link early menarche to lung function deficits in adulthood which may stem from a combination of hormonal, metabolic, or inflammatory factors associated with early menarche. As we did not evaluate these additional hypothesised links in the current study, future studies collecting the necessary data would be key to further understanding these biological and mechanistic pathways. However, existing evidence from biological studies suggests the widespread action of female sex steroid hormones may well play an important role.

There is increasing evidence that female sex steroid hormones are capable of acting directly on various tissues throughout the respiratory tract and further have the potential to modify inflammatory processes associated with respiratory diseases.(25,36) Oestrogen receptors are expressed in airway smooth muscle as well as bronchial and alveolar epithelium where they may play a role in modulating cell proliferation and reactivity to influence the

pathophysiology of chronic lung diseases.(25) Experimental evidence has also demonstrated oestrogen receptor mediated action on inflammatory cells including T-, dendritic and mast cells.(25) Increased levels of female sex steroids (namely oestrogen) are associated with pubertal development and menarche, and it is possible that girls with early menarche experience a larger cumulative exposure to these influential sex hormones as well as the cyclical changes in sex hormones levels associated with menstruation for longer durations when compared to girls with later menarche. A longer reproductive lifespan and cumulative exposure to sex steroid hormones provides some biological plausibility for potential long-term consequences of lesser pulmonary function. Early menarche may even be closely related to coexisting reproductive characteristics (e.g. irregular menstruation), beyond what was available in this study, that negatively influence respiratory health.(11)

Given that childhood growth and metabolic condition have the potential to influence pubertal development, early menarche has been closely linked to increased growth velocity (although not total growth), obesity and insulin resistance.(37–39) Obesity is not only independently related to lung health, but has also been shown to modify or confound the relationship between age at menarche and respiratory disease outcomes.(14,15) Our findings of reduced FRC and spirometric function did not attenuate after adjustment for pre-menarchal childhood BMI, suggesting these associations are not fully explained by metabolic factors.

Most likely, complex combinations of these mechanisms underlie early age at menarche and its implications for subsequent lung health. For this reason, further work into other, non-

height-related, pathophysiological mechanisms is needed to improve our understanding of the relationship between early menarche and adult lung function deficits.

The primary strengths of our study included prospectively collected data on objective outcome measures and key confounders. This was especially true for data on childhood socioeconomic and metabolic indicators as well as repeated measures of both pre- and post-bronchodilator spirometry, which reduce the potential for residual confounding in these analyses and are essential to evaluate mediators.

One important limitation was that age at menarche was collected retrospectively. However, evidence suggests that this is generally a well-remembered event, and in these circumstances, any misclassification would likely be non-differential.(40)

In conclusion, our population-based longitudinal study provides evidence to support the presence of a temporal association between early menarche and lower lung function in middle-age. Our findings also suggest early menarche impacts lung function through its role in influencing adult-attained height, although importantly, this mechanism only explains a portion of the association. While replication of this study is desirable to confirm these findings, our results are generalizable to Caucasian middle-aged women of general populations.

Acknowledgements:

We acknowledge the TAHS study participants and previous investigators. We thank Professor Mark Jenkins, Centre for Epidemiology & Biostatistics, The University of Melbourne, Victoria, a TAHS investigator, but not a co-author of this manuscript, for his assistance with obtaining funds and data collection. We also 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 Mrs Cathryn Wharton and Dr Desiree Mészáros. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 TAHS questionnaires.

This study was supported by the National Health and Medical Research Council (NHMRC) of Australia under NHMRC project grant scheme (299901, 1021275) and NHMRC European collaborative grant scheme (1101313) as part of ALEC (Ageing Lungs in European Cohorts funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 633212); The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline. The funding agencies had no direct role in the conduct of the study, the collection, management, statistical analysis and interpretation of the data, preparation or approval of the manuscript. J.A. Simpson, C Lodge, A Lowe, S C Dharmage are funded by NHMRC Fellowships.

Disclosure statement: M.A. has held investigator initiated grants from Pfizer and Boehringer-Ingelheim for unrelated research. He has also received assistance with conference attendance from Sanofi.

Author contributions:

References

1. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration. *Endocr Rev*. 2003 Oct 1;**24**(5):668–93.

2. Sawyer SM, Afifi RA, Bearinger LH, Blakemore SJ, Dick B, Ezeh AC, Paton GC. Adolescence: a foundation for future health. *Lancet*. 2012 Apr;**379**(9826):1630–40.

3. Abreu AP, Kaiser UB. Pubertal development and regulation. *Lancet Diabetes Endocrinol*. 2016 Mar;**4**(3):254–64.

4. Karapanou O, Papadimitriou A. Determinants of menarche. *Reprod Biol Endocrinol*. 2010 Sep 30;**8**:115.

5. Zein JG, Erzurum SC. Asthma is Different in Women. *Curr Allergy Asthma Rep*. 2015;**15**(6):28.

6. Tam A, Morrish D, Wadsworth S, Dorscheid D, Man SFP, Sin DD. The role of female

hormones on lung function in chronic lung diseases. *BMC Womens Health*. 2011;**11**(1):24.

7. Australian Centre for Asthma Monitoring. Asthma in Australia: with a focus chapter on chronic obstructive pulmonary disease. Asthma series no. 4. Canberra: AIHW. 2011.

8. Lieberoth S, Gade EJ, Brok J, Backer V, Thomsen SF. Age at menarche and risk of asthma: systematic review and meta-analysis. *J Asthma*. 2014;**51**(6):559–65.

9. Macsali F, Svanes C, Bjørge L, Omenaas ER, Gómez Real F. Respiratory health in women: from menarche to menopause. *Expert Rev Respir Med*. 2012;**6**(2):187–202.

10. Matheson MC, Burgess JA, Lau MYZ, Lowe AJ, Gurrin LC, Hopper JL, Giles GG, Johns DP, Walters EH, Abramson MJ, Real FG, Dharmage SC. Hormonal contraception increases risk of asthma among obese but decreases it among nonobese subjects: a prospective, population-based cohort study. *ERJ Open Res*. 2015;**1**(2).

11. Macsali F, Real FG, Plana E, Sunyer J, Anto J, Dratva J, Janson C, Jarvis D, Omenaas ER, Zemp E, Wjst M, Leynaert B, Svanes C. Early age at menarche, lung function, and adult asthma. *Am J Respir Crit Care Med*. 2011;**183**(1):8–14.

12. Gill D, Sheehan NA, Wielscher M, Shrine N, Amaral AFS, Thompson JR, Granell R, Leynaert B, Real FG, Hall IP, Tobin MD, Auvinen J, Ring SM, Jarvelin MR, Wain LV, Henderson J, Jarvis D, Minelli C. Age at menarche and lung function: a Mendelian randomization study. *Eur J Epidemiol*. 2017;**32**(8):701-710.

13. Castro-Rodríguez JA . A new childhood asthma phenotype: obese with early menarche. *Paediatr Respir Rev*. 2016 Mar;**18**:85–9.

14. Varraso R, Siroux V, Maccario J, Pin I, Kauffmann F. Asthma severity is associated with body mass index and early menarche in women. *Am J Respir Crit Care Med*. 2005;**171**(4):334–9.

15. Castro-Rodríguez JA, Holberg CJ, Morgan WJ, Wright AL, Martinez FD. Increased Incidence of Asthmalike Symptoms in School Years. *Am J Respir Crit Care Med*. 2001;**163**(6):1344–9.

16. Ali Z, Ulrik CS. Obesity and asthma: A coincidence or a causal relationship? A systematic review. *Respiratory Medicine*. 2013;**107**(9): 1287–300.

17. Matheson MC, Abramson MJ, Allen K, Benke G, Burgess JA, Dowty JG, Erbas B, Feather IH, Frith PA, Giles GG, Gurrin LC, Hamilton GS, Hopper JL, James AL, Jenkins MA, Johns DP, Lodge CJ, Lowe AJ, Markos J, Morrison SC, Perret JL, Southey MC, Thomas PS, Thompson BR, Wood-Baker R, Walters EH. Cohort Profile: The Tasmanian Longitudinal Health Study (TAHS). *Int J Epidemiol*. 2017 Apr 1;**46**(2):407–408.

18. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CPM, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J, ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005 Aug 1;**26**(2):319–38.

19. Williamson EJ, Aitken Z, Lawrie J, Dharmage SC, Burgess JA, Forbes AB. Introduction to causal diagrams for confounder selection. *Respirology*. 2014 Apr;**19**(3):303–11.

20. Lawlor DA, Ebrahim S, Davey Smith G. Association between self-reported childhood socioeconomic position and adult lung function: findings from the British Women's Heart and Health Study. *Thorax*. 2004 Mar;**59**(3):199–203.

21. Noal RB, Menezes AMB, Macedo SEC, Dumith SC. Childhood body mass index and risk of asthma in adolescence: A systematic review. *Obes Rev*. 2011;**12**(2):93–104.

22. Davidson WJ, Mackenzie-Rife KA, Witmans MB, Montgomery MD, Ball GDC, Egbogah S, et al. Obesity negatively impacts lung function in children and adolescents. *Pediatr Pulmonol*. 2014;**49**(10):1003–10.

23. James-Todd T, Tehranifar P, Rich-Edwards J, Titievsky L, Terry MB. The impact of socioeconomic status across early life on age at menarche among a racially diverse population of girls. *Ann Epidemiol*. 2010 Nov;**20**(11):836–42.

24. Hicks R, Tingley D. Causal mediation analysis. *Stata J*. 2011;**11**(4):609–615.

25. Townsend EA, Miller VM, Prakash YS. Sex differences and sex steroids in lung health and disease. *Endocrine Reviews*. 2012. **33**(1):1-47.

26. Chumlea WC, Schubert CM, Roche AF, Kulin HE, Lee PA, Himes JH, Sun SS. Age at menarche and racial comparisons in US girls. *Pediatrics*. 2003 Jan;**111**(1):110–3.

27. Al-Sahab B, Ardern CI, Hamadeh MJ, Tamim H. Age at menarche in Canada: results from the National Longitudinal Survey of Children & Youth. *BMC Public Health*. 2010 Dec;**10**(1):736.

28. Sun Y, Mensah FK, Azzopardi P, Patton GC, Wake M. Childhood Social Disadvantage and Pubertal Timing: A National Birth Cohort From Australia. *Pediatrics*. 2017; **139**(6).

29. Donohue JF. Minimal clinically important differences in COPD lung function. *COPD*. 2005 Mar;**2**(1):111–24.

30. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal Clinically Important Differences in Pharmacological Trials. *Am J Respir Crit Care Med. American Thoracic Society*; 2014 Feb;**189**(3):250–5.

31. Cazzola M, MacNee W, Martinez FJ, Rabe KF, Franciosi LG, Barnes PJ, Brusasco V, Burge PS, Calverley PM, Celli BR, Jones PW, Mahler DA, Make B, Miravitlles M, Page CP, Palange P, Parr D, Pistolesi M, Rennard SI, Rutten-van Mölken MP, Stockley R, Sullivan SD, Wedzicha JA, Wouters EF; American Thoracic Society; European Respiratory Society Task Force on outcomes of COPD. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008 Feb;**31**(2):416–69.

32. Onland-Moret NC, Peeters PHM, van Gils CH, Clavel-Chapelon F, Key T, Tjønneland A, Trichopoulou A, Kaaks R, Manjer J, Panico S, Palli D, Tehard B, Stoikidou M,

Bueno-De-Mesquita HB, Boeing H, Overvad K, Lenner P, Quirós JR, Chirlaque MD, Miller AB, Khaw KT, Riboli E. Age at Menarche in Relation to Adult Height: The EPIC Study. *Am J Epidemiol*. 2005 Aug 24;**162**(7):623–32.

33. Walvoord EC. The timing of puberty: is it changing? Does it matter? *J Adolesc Health*. 2010 Nov;**47**(5):433–9.

34. Yousefi M, Karmaus W, Zhang H, Roberts G, Matthews S, Clayton B, Arshad SH. Relationships between age of puberty onset and height at age 18 years in girls and boys. *World J Pediatr*. 2013 Aug 18;**9**(3):230–8.

35. Shim KS. Pubertal growth and epiphyseal fusion. *Ann Pediatr Endocrinol Metab*. 2015 Mar;**20**(1):8–12.

36. Haggerty CL, Ness RB, Kelsey S, Waterer G. The impact of estrogen and progesterone on asthma. *Ann Allergy Asthma Immunol*. 2003 Mar;**90**(3):284-91-3, 347.

37. Burt Solorzano CM, McCartney CR. Obesity and the pubertal transition in girls and boys. *Reproduction*. 2010 Sep;**140**(3):399–410.

38. Heys M, Schooling CM, Jiang C, Cowling BJ, Lao X, Zhang W, Cheng KK, Adab P, Thomas GN, Lam TH, Leung GM. Age of Menarche and the Metabolic Syndrome in China. *Epidemiology*. 2007 Nov;**18**(6):740–6.

39. Kaplowitz PB. Link Between Body Fat and the Timing of Puberty. *Pediatrics*. 2008 Feb;**121**:208–17.

40. Must A, Phillips SM, Naumova EN, Blum M, Harris S, Dawson-Hughes B, Rand WM. Recall of early menstrual history and menarcheal body size: after 30 years, how well do women remember? *Am J Epidemiol*. 2002 Apr 1;**155**(7):672–9.

Table 1: Characteristics and demographic data from the 1st, 5th and 6th decade TAHS waves of data collection for the female study population with reported data on age at menarche.

	Age at menarche<12 *n= 423 (16%)* Mean [SD] *% (n)*	**Age at menarche≥12** *n=2298 (84%)* Mean [SD] *% (n)*
1968 Data: Age 7 years		
Height (cm)	121.2 [5.10]	119.8 [4.86]
Weight (kg)	24.1 [3.20]	22.8 [2.92]
BMI (z-score)	0.41 [0.71]	0.17 [0.73]
Litres FEV_1 *FVC*	 1.31 [0.22] 1.44 [0.23]	 1.29 [0.21] 1.39 [0.22]
Paternal smoking	*62.5 (250)*	*60.7 (1307)*
Maternal smoking	*38.2 (154)*	*35.0 (768)*
SES 1968 *(1) Manager/Admin* *(2) Associate Professional* *(3) Tradespersons* *(4) Production/Sales/Clerical* *(5) Laborer/ house person*	 *21.0 (86)* *8.3 (34)* *28.1 (115)* *31.0 (127)* *11.7 (48)*	 *23.0 (498)* *7.0 (151)* *29.4 (636)* *26.8 (581)* *13.8 (299)*
2006 Data: Mean Age 45 years		
Height (cm)	162.4 [5.78]	163.9 [5.89]
Weight (kg)	80.7 [21.91]	75.3 [18.75]
BMI (kg/m^2)	30.5 [8.05]	28.1 [7.14]
Ever smoker	*60.5 (256)*	*59.8 (1367)*
Current smoker	*33.8 (143)*	*29.0 (663)*
2016 Data: Mean Age 53 years		
Height (cm)	162.2 [6.71]	163.9 [6.72]
Weight (kg)	78.6 [17.64]	74.9 [16.24]
BMI (kg/m^2)	30.0 [6.44]	27.9 [7.23]
Ever smoker	*55.6 (144)*	*55.0 (751)*
Current smoker	*18.5 (48)*	*15.0 (205)*

BMI- body mass index
SES- socioeconomic status

Table 2: Pre & post-bronchodilator spirometric and static lung volume outcomes at mean ages 45 & 53 years with respect to age at menarche (<12 vs ≥12 years reference group).

	Age 45		Age 53	
	≥12 years reference value	**Mean difference**	***≥12 years reference value***	**Mean difference**
Pre-BD **FEV_1**	2.85 (2.81, 2.89)	-143 (-246, -40) p=0.007	2.74 (2.71, 2.77)	-154 (-221, -87) p<0.001
FVC	3.70 (3.65, 3.75)	-217 (-339, -95) p=0.001	3.53 (3.50, 3.56)	-234 (-314, -155) p<0.001
FEV_1/FVC	77.0 (76.4, 77.6)	0.68 (-0.92, 2.3) p=0.405	77.6 (77.2, 78.0)	0.98 (0.008,1.9) p= 0.048
Post-BD **FEV_1**	2.94 (2.90, 2.98)	-133 (-233, -33) p=0.009	2.83 (2.80, 2.86)	-171 (-236, -106) p<0.001
FVC	3.71 (3.66, 3.75)	-183 (-300, -65) p=0.002	3.55 (3.51, 3.58)	-251 (-329, -174) p<0.001
FEV_1/FVC	79.4 (78.8, 80.0)	0.55 (-0.97, 2.08) p=0.476	80.0 (79.6, 80.4)	0.89 (-0.02, 1.80) p= 0.056
TLC	5.60 (5.46, 5.74)	-260 (-616, 97) p=0.153	-	-
RV	1.77 (1.72, 1.81)	-100 (-216, 17) p=0.095	-	-
RV/TLC	31.11 (30.49, 31.73)	0.09 (-1.45, 1.63) p=0.905	-	-
FRC	2.79 (2.73, 2.85)	-168 (-315, -21) p=0.025	-	-

() – 95% Confidence Interval
Reference values for FEV_1 and FVC presented in litres (L) and mean difference presented in millilitres (mL); FEV_1/FVC reference values and mean differences expressed as percentages.
Number in analyses: 45 year pre-BD spirometry (n=581); 45 year post-BD spirometry (n=572); 45 year lung volumes (n=517); 53 year pre-BD spirometry (n=1114); 53 year post-BD spirometry (n=1100)
Adjusted for: Parental smoking, Pre-menarchal SES, Pre-menarchal asthma, Pre-menarchal weight (age 7 years)

Table 3: Direct and indirect effects (via adult attained height) of age at menarche (<12 years vs ≥12 years) on pre- and post-bronchodilator lung function outcomes at age 53 years and functional residual capacity at age 45 years.

	Indirect effect, mL	*Direct effect, mL*	*Total effect, mL*	*% mediated by height*	*Correlation in error terms**
Pre-BD					
FEV_1	-68 (-91, -44)	-85 (-148, -20)	-153 (-217, -88)	44 (31, 77)	0.35
FVC	-99 (-133, -66)	-133 (-205, -59)	-233 (-308, -157)	43 (32, 63)	0.43
Post-BD					
FEV_1	-72 (-96, -47)	-99 (-159, -36)	-170 (-233, -108)	42 (31, 66)	0.37
FVC	-101 (-135 -67)	-149 (-218, -77)	-250 (-323, -177)	40 (31, 57)	0.44
FRC	-102 (-155, -51)	-66 (-203, 76)	-168 (-309, -26)	60 (32, 100†)	0.35

() – 95% Confidence Interval
*Estimated correlation between the error terms of the mediator and outcome models when % mediated by height=0
†Upper estimate truncated at 100%
Adjusted for: Parental smoking, Pre-menarchal SES, Pre-menarchal asthma, Pre-menarchal weight (age 7 years)

Figure 1: Tasmanian Longitudinal Health Study female study population 1968-2016.