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ORIGINAL ARTICLE

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

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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 = 8583), 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 (BD) forced expiratory volume in 1 s (adjusted mean difference: −133 mL; 95% CI: −233, −33), forced vital capacity (−183 mL; 95% CI: −300, −65) and functional residual capacity (−168 mL; 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-BD outcomes and quantify the partial role of adult height in this association.**

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.

Key words: cohort studies, epidemiology, longitudinal studies, menarche, pulmonary function tests.

INTRODUCTION

Secular trends have suggested a decreasing age at menarche and pubertal onset over recent decades.[1,2] It has

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been hypothesized 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 (BD) forced expiratory volume in 1 s (FEV_1; −113 mL; 95% CI: −196, −33) and forced vital capacity (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 randomization study by Gill *et al.* utilized age at menarche single nucleotide polymorphism (SNP) and found genetic proxies for menarchal age to be associated with short-term improvements in pre-BD 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 have not been previously investigated. This includes serial post-BD spirometry, which has the potential to capture post-BD airflow limitation characteristic of chronic obstructive pulmonary disease (COPD) and detect lung function (LF) decline, along with lung volumes, and 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 hypothesized that an early age at menarche was associated with reduced pre- and post-BD lung function in middle age and that these relationships might be mediated through adult-attained height, weight or asthma. Utilizing 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 TAHS have been fully described previously.[17] Briefly, the baseline TAHS survey was conducted in 1968 and enrolled 8583 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-BD spirometry.

The analyses performed here focused on participants (Fig. 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, 3510 female participants were traced (83.7% of females from the original cohort). Of those, 2776 (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_LCO). During the 6th Decade follow-up, 2965 female participants were invited to take part in the clinical study of whom 1382 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 min after the administration of 300 μg of salbutamol.

During the 5th Decade follow-up, age at menarche was reported by 2721 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 = 1235) and T_LCO (n = 1192) (Fig. 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 T_LCO. Rates of lung function decline from the fifth to sixth

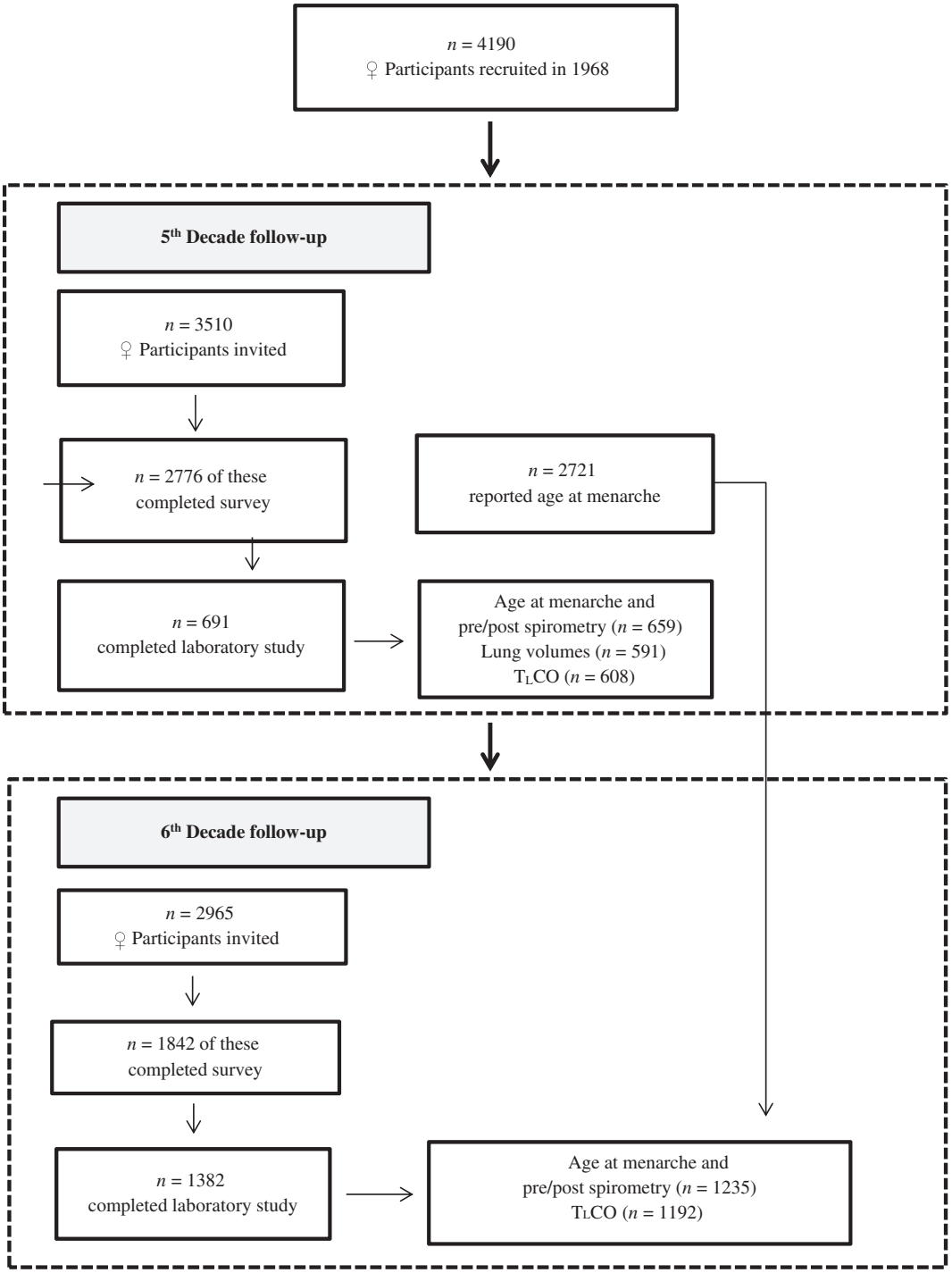

Figure 1 Tasmanian Longitudinal Health Study female study population during 1968–2016. T_LCO, diffusing capacity of the lungs for carbon monoxide.

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 5th 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 categorized 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 the hypothesized causal relationships between age at menarche, lung function and relevant covariates.[19] Parental smoking and pre-menarchal socio-economic status (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 measure, 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, TX, USA).

RESULTS

Sample characteristics and age at menarche

Of the 2721 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% (2298) 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 7 years (121.2 vs 119.8 cm) and had minimally higher pre-menarchal lung function (FEV_1: 1.31 vs 1.29 L; FVC: 1.44 vs 1.39 L) (Table 1). A subsample (n = 272) of these participants was also followed up in 1974 (age 13 years) at which time girls with early menarche also had marginally better lung function (FEV_1: 3.05 vs 2.86 L; FVC: 3.28 vs 3.10 L). As adults, women whose age at menarche was <12 years were shorter (162.4 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 and 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 −133 mL (95% CI: −233, −33; P = 0.009) and −183 mL (95% CI: −300, −65; P = 0.002), respectively, at age 45 years. At 53 years of age, early menarche was associated with a similar reduction in post-BD FEV_1 (−171 mL; 95% CI: −236, −106; P < 0.001) and FVC (−251 mL; 95% CI: −329, −174; P < 0.001).

Early menarche was also associated with a statistically significant reduction in FRC (−168 mL; 95% CI: −315, −21; P = 0.025), although reductions in RV (−100 mL; 95% CI: −216, 17; P = 0.095) and TLC (−260 mL; 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 did not materially change the presented estimates. In addition, no difference in FEV_1/FVC ratio was observed between early and late menarche groups at the 5th Decade follow-up, but a modest positive difference was observed in the 6th Decade (Table 2).

There were no associations between early menarche and T_LCO or lung function decline (mL/year) between the 5th and 6th Decade follow-ups (Table S1 in Supplementary Information).

Association between age at menarche and 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% (−72 mL; 95% CI: −96, −47) of the total effect of early menarche on post-BD FEV_1, 40% of the total effect (−101 mL; 95% CI: −135, −67) for FVC and 60% (−102 mL; 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

Table 1 Characteristics and demographic data from the first, fifth and sixth 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%)	Age at menarche ≥ 12 *n* = 2298 (84%)
	Mean (SD)	Mean (SD)
	% (*n*)	% (*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	1.31 (0.22)	1.29 (0.21)
FVC	1.44 (0.23)	1.39 (0.22)
Paternal smoking	62.5 (250)	60.7 (1307)
Maternal smoking	38.2 (154)	35.0 (768)
SES 1968		
Manager/admin	21.0 (86)	23.0 (498)
Associate professional	8.3 (34)	7.0 (151)
Tradespersons	28.1 (115)	29.4 (636)
Production/sales/clerical	31.0 (127)	26.8 (581)
Labourer/house person	11.7 (48)	13.8 (299)
2006 Data: mean age of 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 of 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; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SES, socio-economic status; TAHS, Tasmanian Longitudinal Health Study.

between early menarche and post-BD 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_LCO) 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 socio-economic 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 randomization observations on early menarche and impairments in FVC, strengthen the existing evidence to support this relationship.[12]

Although our observations were largely consistent with Macsali *et al.*'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

Table 2 Pre- and post-BD spirometric and static lung volume outcomes at mean ages of 45 and 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), $P = 0.025$	—	—

Values in parentheses indicate 95% CI. 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 and pre-menarchal weight (age 7 years).

BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; RV, residual volume; SES, socio-economic status; TLC, total lung capacity.

Table 3 Direct and indirect effects (via adult-attained height) of age at menarche (<12 vs ≥12 years) on pre- and post-BD lung function outcomes at age 53 years and FRC 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

Values in parentheses indicate 95% CI. Adjusted for: parental smoking, pre-menarchal SES, pre-menarchal asthma and pre-menarchal weight (age 7 years).

[†]Estimated correlation between the error terms of the mediator and outcome models when % mediated by height = 0.

[‡]Upper estimate truncated at 100%.

BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; SES, socio-economic status.

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 that 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 100–140 mL for an MCID and also suggested that regulators consider a 5–10% change in FEV_1 from baseline as clinically important, with <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, was 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 hypothesized 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 that 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 provide 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 socio-economic and metabolic indicators as well as repeated measures of both pre- and post-BD 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.

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Abbreviations: BD, bronchodilator; DAG, directed acyclic graph; FEV_1, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; MCID, minimal clinically important difference; RV, residual volume; SES, socio-economic status; TAHS, Tasmanian Longitudinal Health Study; TLC, total lung capacity; T_LCO, diffusing capacity of the lungs for carbon monoxide.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Table S1. Pre- and post-bronchodilator spirometric decline from the 5th Decade TAHS follow-up to the 6th Decade TAHS follow-up with respect to age at menarche (<12 vs ≥12 years).