



The Mediating Role of Body Mass Index in the Association Between Age at First Childbirth and Lung Function Among Chinese Postmenopausal Women

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Objective: Little is known about the effect of age at first childbirth on lung function. We aimed to investigate the association between age at first childbirth and lung function in Chinese women and further test whether this association is mediated by body mass index (BMI).

Methods: This cross-sectional study is a partial survey of the China Kadoorie Biobank (CKB) which was conducted in Xinxiang City, Henan Province between 2004 and 2008. A total of 16,584 postmenopausal women aged 30–79 years were enrolled. Multiple linear and logistic regression were used to investigate the association between age at first childbirth and lung function and overweight/obesity. The mediation analysis was performed using the PROCESS procedure for SPSS.

Results: The mean (SD) age at first childbirth was 23.1 (2.7) years. Women with first childbirth aged ≤ 19 years and 20–22 years had lower lung function than women who gave first childbirth aged 23–25 years. Per 1-year increase in the age at first childbirth was associated with a 3.31 mL increase in FEV1 (95% CI = 1.27–5.35), 3.91 mL increase in FVC (95% CI = 1.63–6.18), 0.15% increase in FEV1, % predicted (95% CI = 0.05–0.24) and 0.14% increase in FVC, % predicted (95% CI = 0.05–0.22). There was no clear association between age at first childbirth and FEV1/FVC ratio. BMI played a contribution to the association between age at first childbirth and FEV1 and the proportion was 16.4% (indirect effect: $\beta = 0.65$, 95% CI = 0.46–0.89; total effect: $\beta = 3.96$, 95% CI = 1.92–5.99). Similarly, the proportion to FVC, FEV1, % predicted, and FVC, % predicted was 25.0%, 16.6%, and 25.0%, respectively.

Conclusion: Early age at first childbirth was associated with lower lung function and BMI mediated the association. It is important to test lung function and popularize the knowledge of weight control in women who gave first childbirth at an early age.

Keywords: first childbirth, lung function, body mass index, mediation, postmenopausal women

Introduction

Chronic respiratory diseases (CRDs) include chronic obstructive pulmonary disease, asthma, occupational lung diseases, and pulmonary hypertension. These common diseases continue to be the leading cause of death and disability worldwide. An estimated 544.9 million people worldwide had chronic respiratory diseases in 2017, representing an increase of 39.8% compared with 1990.¹ In China, approximately 1.1 million Chinese people died of CRDs in 2019, which accounted for 27.3% of CRD deaths in the world.² It is critical to identify the potential risk factors for the prevention of respiratory diseases.

Impaired lung function is a sign of early respiratory injury and plays an important role in the diagnosis of respiratory diseases. Previous studies have reported that several unique factors in women were associated with impaired lung

function including early age at menarche,³ menopause,⁴ multiparity,⁵ and hormone replacement therapy (HRT).⁶ However, whether age at first childbirth is associated with lung function remains uncertain.

Age at first childbirth is a critical point for a woman which represents socio-environmental and physiological transitions in a woman's life. Many studies have found that age at first childbirth was connected with a woman's long-term health outcomes such as mortality,⁷ diabetes,⁸ hypertension,⁹ and depression.¹⁰ Several studies have also indicated that early age at first childbirth was associated with a higher risk of lung diseases.^{11,12} However, to our knowledge, only one study has investigated the association between age at first childbirth and lung function. This study found that age at first childbirth was an independent predictor of lung function. This association was only significant in the leanest category (BMI <25 kg/m²).¹³ Given that obesity was a risk factor for lung function^{14,15} and age at first childbirth was associated with obesity.^{16,17} Moreover, the association between age at first childbirth and lung function has never been discussed in Chinese women. We conducted this study to investigate the association between age at first childbirth and lung function and further test whether the association is mediated by body mass index in a large population of Chinese postmenopausal women.

Methods

Study Design and Participants

The China Kadoorie Biobank (CKB) is a large blood-based prospective study which is conducted in 5 urban and 5 rural regions of China. Regions were chosen according to local disease patterns, exposure to certain risk factors, population stability, quality of death and disease registries, local commitment, and capacity. A detailed introduction to the CKB study can be found in three published articles.^{18–20} Briefly, this cross-sectional analysis is based on the baseline data derived from Xinxiang City, Henan Province, which is one of the five rural regions of the CKB study. At baseline, a total of 63,357 participants aged 30–79 years completed the questionnaires and physical examinations. It typically took 35–45 minutes to complete the information for each participant. There were 27,842 men and 35,515 women accounting for 44.0% and 56.0%, respectively. We excluded men, pre-/perimenopausal women, participants without data of age at first childbirth, and participants with tuberculosis/emphysema/bronchitis/asthma, 16,584 postmenopausal women were included in the final analysis. All procedures in our study were in line with the Declaration of Helsinki. All participants provided written informed consent. The study was approved by the ethics committees of the University of Oxford and the Chinese Center for Disease Control and Prevention (CDC). Ethics approval was also obtained from the institutional research board at the Henan Provincial CDC and Huixian CDC.

Age at First Childbirth Assessment

Trained health workers asked women “How many live births have you had so far?”. If women reported the number of live births, the workers would further ask “How old are you when you give each birth?”. Then, the workers recorded it on the laptop-based questionnaires. In this analysis, we classified age at first childbirth into 4 groups (≤ 19 , 20–22, 23–25, ≥ 26 years) and regarded 23–25 years as the reference category.¹³ Age at first childbirth was also included in our analysis as a continuous variate.

Lung Function Measurement

We used five indicators to evaluate lung function including forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC ratio, FEV1, % predicted and FVC, % predicted. FEV1 and FVC were measured twice using a standard spirometry instrument, and the maximum values were used in this analysis. FEV1, % predicted and FVC, % predicted are standardized spirometric parameters according to participants' age, height, and weight. They were calculated using a standard spirometry instrument. FEV1 is a measurement of how much air can be forcefully exhaled in one second and FVC is a measurement of lung size. A low FVC may be caused by either obstructive or restrictive diseases. A low FEV1 can be caused by obstructive and restrictive lung diseases. FEV1/FVC ratio is a better clinical indicator to distinguish obstructive and restrictive lung diseases than FEV1.

Covariates Definitions

The interviewer-administered electronic questionnaire was used to collect data on sociodemographic characteristics, lifestyle factors, and reproductive history by well-trained workers. Sociodemographic characteristics included age at baseline, marital status (married, unmarried), educational level (no formal school, primary school, middle school, high school or above), and household income (<5000, 5000–9999, 10,000–19,999, $\geq 20,000$). Lifestyle factors included drinking (never, ex-regular/occasional, current regular drinking) and smoking (never, ex-regular/occasional, current regular smoking). A day's work and leisure activities of participants were transformed into the Metabolic Equivalent of Task value (MET-hours/day). Reproductive factors contained parity (1–2, 3–4, ≥ 5), age at menopause (≤ 42 , 43–52, ≥ 53 years), natural menopause (no, yes), and use of the oral contraceptive pill (no, yes). Height and weight were measured using calibrated instruments according to standardized protocols. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared. As recommended by the Working Group on Obesity in China, we defined overweight as BMI = 24.0–27.9 kg/m² and obesity as BMI ≥ 28.0 kg/m².²¹

Statistical Analysis

Continuous variables were presented as the mean [standard deviation (SD)], and categorical variables were shown as a number with percentages [n (%)]. A multivariate linear regression model was used to estimate the beta coefficients (β) and 95% confidence intervals (CIs) between age at first childbirth and lung function. We adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, height, BMI, age at menopause, type of menopause, parity, and oral contraceptive pill use in the multivariate linear model. We also used the multivariate logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) between age at first childbirth and overweight/obesity. For the first logistic regression model, we adjusted for age at baseline. In model 2, we adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, and physical activity. Then, we adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, age at menopause, type of menopause, parity, and oral contraceptive pill use in model 3. Mediation analysis was conducted using the PROCESS procedure for SPSS. The mediation analysis also adjusted for potential confounders: age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, height, age at menopause, type of menopause, parity, and oral contraceptive pill use. Briefly, there are four steps for the analysis: 1) estimating the total effect of age at first childbirth on lung function (Path c), without adjustment for BMI. 2) showing the direct effect of age at first childbirth on lung function (Path c') and BMI on lung function (Path b), with adjustment for BMI. 3) showing the effect of age at first childbirth on BMI (Path a). 4) determining the proportion of the mediation effect by calculating the indirect effect (a*b)/total effect (c). We conducted all analysis using SPSS Version 25.0.

Results

Participants Characteristics

Table 1 shows the baseline characteristics of women according to age at first childbirth. Among the 16,584 postmenopausal women, the mean (SD) age at baseline was 58.4 (7.3) years, the mean (SD) age at first childbirth was 23.1 (2.7) years, the mean (SD) BMI was 24.7 (3.7) kg/m², mean (SD) FEV1 was 2031 (435) mL, and mean (SD) FVC was 2495 (489) mL. A few women were current regular smoking (0.5%), current regular drinking (2.3%), and ever taking oral contraceptives (4.5%). Compared with women who gave the first childbirth at a later age, women with an earlier age at first childbirth were older, less educated, had lower household income, had higher parity and BMI, and were more likely to have lower FEV1, FVC, FEV1/FVC ratio, FEV1, % predicted and FVC, % predicted.

Age at First Childbirth and Lung Function

The association between age at first childbirth and lung function is presented in Table 2. Women with first childbirth aged ≤ 19 years and 20–22 years had lower lung function than women who gave first childbirth aged 23–25 years: FEV1 was 21.75 mL (95% CI = –41.72, –1.79) and 20.84 mL (95% CI = –33.18, –8.50) lower; FVC was 21.20 mL (95% CI = –49.47, –4.93) and 24.03 mL (95% CI = –37.80, –10.26) lower; FEV1, % predicted was 0.89% (95% CI = –1.80–0.03)

Table 1 Characteristics of Participants According to Age at First Childbirth

Variables	Age at First Childbirth(Years)				
	≤19 (N=1463)	20–22 (N=5669)	23–25 (N=6580)	≥26 (N=2872)	Overall (N=16584)
Age (years), mean (SD)	63.7(6.8)	60.5(7.2)	56.4(6.9)	56.0(5.8)	58.4(7.3)
Marital status, n (%)					
Married	1036(70.8)	4640(81.8)	5919(90.0)	2650(92.3)	14,245(85.9)
Unmarried	427(29.2)	1029(18.2)	661(10.0)	222(7.7)	2339(14.1)
Educational level, n (%)					
No formal school	718(49.1)	2005(35.4)	1926(29.3)	761(26.5)	5410(32.6)
Primary school	658(45.0)	3002(53.0)	3361(51.1)	1534(53.4)	8555(51.6)
Middle school	78(5.3)	548(9.6)	988(15.0)	431(15.0)	2045(12.3)
High school or above	9(0.6)	114(2.0)	305(4.6)	146(5.1)	574(3.5)
Household income, n (%)					
<5000	658(45.0)	1882(33.2)	1102(16.7)	351(12.2)	3993(24.1)
5000–9999	225(15.4)	1268(22.4)	1664(25.3)	798(27.8)	3955(23.9)
10,000–19,999	479(32.7)	2049(36.1)	3045(46.3)	1326(46.2)	6899(41.5)
≥20,000	101(6.9)	470(8.3)	769(11.7)	379(13.8)	1737(10.5)
Drinking, n (%)					
Never	503(34.4)	1794(31.6)	1841(28.0)	833(29.0)	4971(30.0)
Ex-regular/Occasional	924(63.1)	3732(65.9)	4592(69.8)	1979(68.9)	11,227(67.7)
Current regular	36(2.5)	143(2.5)	147(2.2)	60(2.1)	386(2.3)
Smoking, n (%)					
Never	1424(97.3)	5581(98.5)	6491(98.6)	2848(99.2)	16,344(98.5)
Ex-regular/Occasional	23(1.6)	58(1.0)	64(1.0)	17(0.6)	162(1.0)
Current regular	16(1.1)	30(0.5)	25(0.4)	7(0.2)	78(0.5)
Age at menopause (years), n (%)					
≤42	194(13.3)	681(12.0)	737(11.2)	262(9.1)	1874(11.3)
43–52	1031(70.5)	4171(73.6)	5196(79.0)	2345(81.7)	12,743(76.8)
≥53	238(16.2)	817(14.4)	647(9.8)	265(9.2)	1967(11.9)
Natural menopause, n (%)					
Yes	1399(95.6)	5356(94.5)	6169(93.8)	2720(94.7)	15,644(94.3)
No	64(4.4)	313(5.5)	411(6.2)	152(5.3)	940(5.7)
Parity, n (%)					
1–2	60(4.1)	628(11.1)	1321(20.1)	759(26.4)	2768(16.7)
3–4	475(32.5)	2631(46.4)	3315(50.4)	1442(50.2)	7863(47.4)
≥5	928(63.4)	2410(42.5)	1944(29.5)	671(23.4)	5953(35.9)
Ever use of oral contraceptive pill, n (%)					
No	1425(97.4)	5428(95.7)	6252(95.0)	2735(95.2)	15,840(95.5)
Yes	38(2.6)	241(4.3)	328(5.0)	137(4.8)	744(4.5)
BMI (kg/m ²), mean (SD)	25.3(4.0)	24.9(3.8)	24.6(3.6)	24.4(3.5)	24.7(3.7)
Physical activity, MET (h/d), mean (SD)	10.9(6.9)	12.1(7.3)	14.1(8.8)	14.7(9.1)	13.2(8.3)
Height (m), mean (SD)	1.5(0.1)	1.5(0.1)	1.5(0.1)	1.5(0.1)	1.5(0.1)
FEV1 (mL), mean (SD)	1850(432)	19501(435)	2102(425)	2118(400)	2031(435)
FVC (mL), mean (SD)	2293(481)	2406(485)	2573(481)	2594(457)	2495(489)
FEV1/FVC ratio, mean (SD)	80.4(6.0)	80.8(5.8)	81.5(5.3)	81.6(5.2)	81.2(5.5)
FEV1, % predicted, mean (SD)	88.9(16.9)	90.0(16.0)	92.0(15.1)	92.5(14.4)	91.1(15.5)
FVC, % predicted, mean (SD)	88.2(14.8)	89.3(14.1)	91.1(13.7)	91.6(13.1)	90.3(13.9)

Note: Data are shown as mean ± SD for continuous variables and n (%) for categorical variables.

Abbreviations: SD, standard deviation; BMI, body mass index; MET, metabolic equivalent of the task; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

and 0.91% (95% CI = −1.48, −0.35) lower. FVC, % predicted was 0.94% (95% CI = −1.76, −0.12) and 0.85% (95% CI = −1.35, −0.34) lower. When we considered the age at first childbirth as a continuous variable, per 1-year increase in age at first childbirth was associated with a 3.31 mL increase in FEV1 (95% CI = 1.27–5.35), 3.91 mL increase in FVC (95%

Table 2 Association Between Age at First Childbirth and Lung Function

Lung Function	β (95% CI) ^a				
	≤19 Years (N=1463)	20–22 Years (N=5669)	23–25 Years (N=6580)	≥26 (Years)(N=2872)	Per 1-Year Increase
FEV1, mL	-21.75 (-41.72, -1.79)	-20.84 (-33.18, -8.50)	Ref.	4.73 (-9.90, 19.37)	3.31 (1.27, 5.35)
FVC, mL	-21.20 (-49.47, -4.93)	-24.03 (-37.80, -10.26)	Ref.	7.69 (-8.64, 24.01)	3.91 (1.63, 6.18)
FEV1/FVC ratio	0.04 (-0.28, 0.36)	-0.07 (-0.26, 0.13)	Ref.	0.01 (-0.22, 0.25)	0.02 (-0.02, 0.05)
FEV1, % predicted	-0.89 (-1.80, 0.03)	-0.91 (-1.48, -0.35)	Ref.	0.22 (-0.45, 0.89)	0.15 (0.05, 0.24)
FVC, % predicted	-0.94 (-1.76, -0.12)	-0.85 (-1.35, -0.34)	Ref.	0.26 (-0.34, 0.86)	0.14 (0.05, 0.22)

Note: ^aMultivariable linear regression model adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, height, body mass index, age at menopause, type of menopause, parity, and oral contraceptive pill use.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; CI, confidence interval.

CI = 1.63–6.18), 0.15% increase in FEV1, % predicted (95% CI = 0.05–0.24) and 0.14% increase in FEV1, % predicted (95% CI = 0.05–0.22). There was no clear association between age at first childbirth and FEV1/FVC ratio.

Age at First Childbirth and Overweight/Obesity

Table 3 shows the adjusted odds ratios (ORs) between age at first childbirth and overweight/obesity. After adjustment for age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, age at menopause, type of menopause, parity, and oral contraceptive pill use, women who gave first childbirth at age ≤19 years, 20–22 years, and ≥26 years, had 1.40 times (95% CI, 1.24–1.58), 1.19 times (95% CI, 1.10–1.28) and 0.86 times (95% CI, 0.79–0.94), respectively, higher risk of overweight/obesity compared with women who gave first childbirth aged 23–25 years. Per-1-year increase of age at first childbirth was associated with a 5% decreased risk of overweight/obesity (95% CI = 0.94–0.96).

Mediation Effect of BMI

Figure 1 shows the results of the mediation analysis after adjusting for all potential covariates. The results indicated that per-year delay in age at first childbirth was significantly associated with an increase of 3.96 mL in FEV1 (total effect, 95% CI: 1.92, –5.99). Among the 3.96 mL increase in FEV1, an increase of 0.65 mL (indirect effect, 95% CI: 0.46–0.89) was attributable to a decrease in the BMI (0.12 kg/m², 95% CI –0.15– –0.10) for each year delay in age at the first childbirth. The proportion of the mediation effect of BMI was 16.4%. Similarly, the contribution of BMI to the association between age at first childbirth and FVC, FEV1, % predicted, and FVC, % predicted was 25.0%, 16.6%, and 25.0%, respectively.

Discussion

In this study, we explored the association between age at first childbirth and lung function and the mediating role of BMI on this association. We observed that early age at first childbirth was significantly associated with lower FEV1, FVC,

Table 3 Association Between Age at First Childbirth and Overweight/Obesity

Variables	Age at First Childbirth(Years)				
	≤19(N=1463)	20–22 (N=5669)	23–25 (N=6580)	≥26 (N=2872)	Per 1-Year Increase
Overweight/Obesity cases	887	3283	3642	1479	
Prevalence (%)	60.6	57.9	55.4	51.5	
Model 1	1.45(1.28, 1.63)	1.21(1.12, 1.30)	Ref.	0.85(0.78, 0.93)	0.94(0.93, 0.95)
Model 2	1.44(1.27, 1.62)	1.20(1.11, 1.29)	Ref.	0.86(0.78, 0.94)	0.95(0.93, 0.96)
Model 3	1.40(1.24, 1.58)	1.19(1.10, 1.28)	Ref.	0.86(0.79, 0.94)	0.95(0.94, 0.96)

Notes: Data are odds ratios (95% confidence intervals). Model 1, adjusted for age at baseline; Model 2, adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, and physical activity; Model 3, adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, age at menopause, type of menopause, parity, and oral contraceptive pill use.

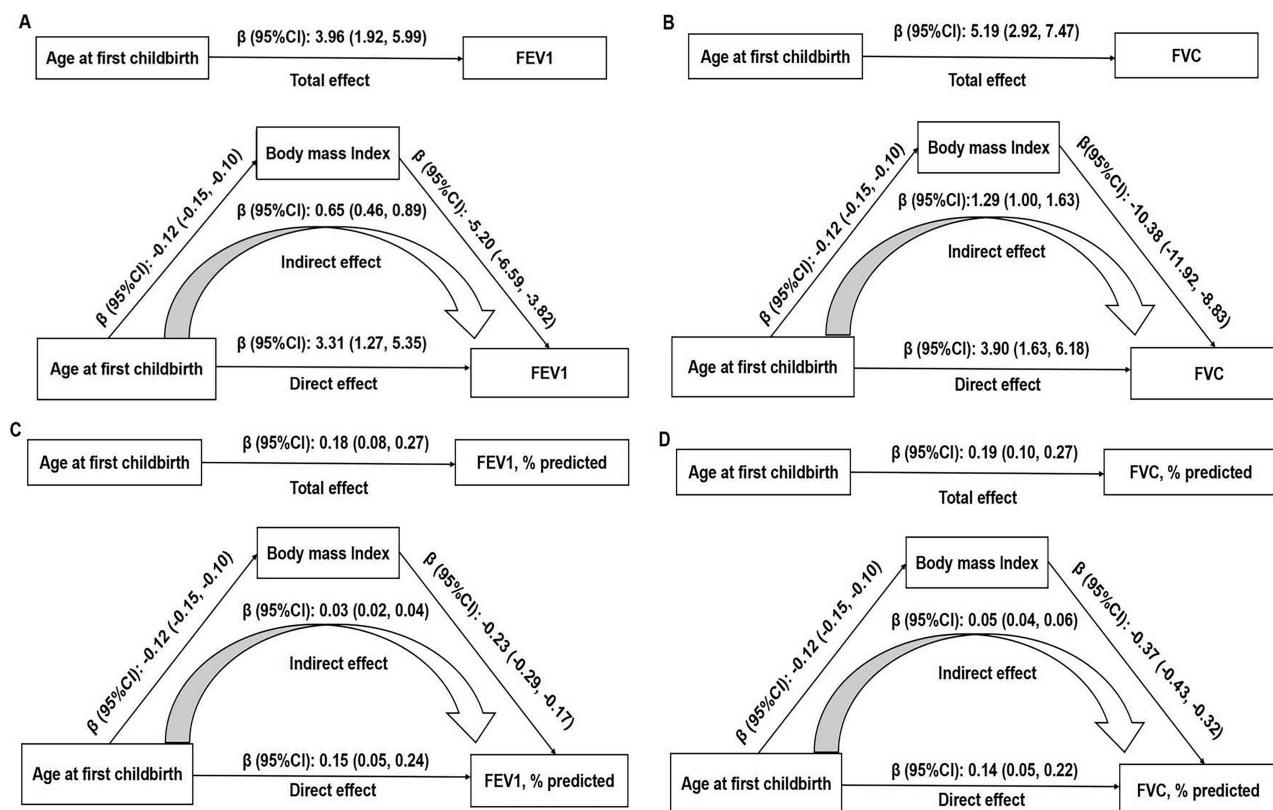


Figure 1 Mediation effect of body mass index on the association between age at first childbirth and lung function. (A) FEV1; (B) FVC; (C) FEV1, % predicted; (D) FVC, % predicted.

Note: Mediation analysis was adjusted for age at baseline, marital status, educational level, household income, drinking, smoking, physical activity, height, age at menopause, type of menopause, parity, and oral contraceptive pill use.

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; β , beta coefficient; CI, confidence interval.

FEV1, % predicted and FVC, % predicted but not with FEV1/FVC ratio. In addition, BMI played a contribution to the association between age at first childbirth and lung function. The proportion of mediation effect was 16.4%, 25.0%, 16.6%, and 25.0%, respectively.

The relationship between age at first childbirth and lung function has been less explored. To our knowledge, a cross-sectional study of 1106 premenopausal and postmenopausal women found that early age at first childbirth was associated with lower FEV1 and FVC, which is consistent with our results.¹³ However, this study was conducted in Isparta and Turkey and did not explore the exact role of obesity on this association. The results of our study on the association between the age at first childbirth and lung function answered such an important issue in the Chinese population.

In our study, women who gave first birth at an early age had a higher risk of obesity, which is in line with the previous studies. A nationally representative longitudinal study found that women who experienced their first birth aged ≤ 21 years had a BMI 5 units greater than women who delayed childbearing until at least age 30.²² The Baltimore Midlife Women's Health Study also reported that each 1-year increase in age at first birth was associated with 3% and 5% lower odds of becoming overweight/obese in midlife.¹⁶ This association between age at first childbirth and obesity could be due to adverse lifestyle changes after giving birth to the first child. Most pregnant women tended to have a higher intake of fat and lower physical activity compared with the pre-pregnancy.^{23,24} Increased energy intake or adaptive changes in energy expenditures in pregnancy may lead to gestational weight gain.^{25,26} Teenage pregnancies especially tended to have higher weight gain and have difficulty in losing the weight gain during pregnancy and returning to their pre-pregnancy weight than adult pregnancies.^{27,28} Women who gained excess weight during pregnancy had increased odds of long-term maternal overweight and obesity.²⁹ That may be why women with an early age of childbirth were still associated with a higher risk of obesity even after adjustment for parity and other potential confounders.

Though the mechanisms between early age at first childbirth and lower lung function are unclear, the mediating role of obesity indicated that age at first childbirth may affect lung function partially through obesity. On the one hand, excessive accumulation of fat deposits in the mediastinum and the abdominal cavities reduce the compliance of the lungs, chest wall, and entire respiratory system.³⁰ On the other hand, low-grade inflammation of the pulmonary spirometry and pulmonary vascular function was induced in adipose tissue which led to the impairment of lung function.³¹ Finally, several studies also indicated that obesity-induced insulin resistance should also be considered the contributing factor to the decline in lung function.^{32,33}

Partial mediation of obesity also suggested that other potential variables beyond adiposity can mediate the effect of age at first childbirth on lung function. We observed that women with an early age at first childbirth (≤ 22 years) were more likely to have lower household income and lower educational levels. The Australian Longitudinal Study on Women's Health reported that social disadvantage predisposes women to become mothers early and adopt unhealthy behaviors.³⁴ A population-based cohort of 1458 individuals indicated that a life-course disadvantaged SES was an important predictor of lower lung function during adulthood.³⁵ Besides, pregnant teenagers are more likely to suffer from preeclampsia compared with their older counterparts. Preeclampsia is significantly associated with alterations in the respiratory system.^{36,37}

Several strengths of our study are as follows. First, to our knowledge, this is the first comprehensive analysis of the association between age at first childbirth and lung function among such a large population of Chinese women. Second, our study verified the mediating role of obesity which provided evidence of a potential mechanism in the association between age at first childbirth and lung function. Some limitations are also included in our study. First, age at first childbirth was collected through self-reports, which may cause recall bias. Second, we cannot rule out unmeasured and residual confounding though we have adjusted for a series of possible confounders. Third, the study only included participants living in Xinxiang City, Henan Province, who were selected according to the cluster sampling method. In addition, age 19 is a critical age for women who gave their first childbirth.¹³ The size of women with first childbirth aged ≤ 19 years was small in our study. Future studies are needed to confirm our findings among diverse populations. Additional studies are also needed to clarify other mechanisms that link age at first childbirth to lung function.

In conclusion, our study demonstrated that early age at first childbirth was associated with lower lung function and this association was partially mediated by BMI. It is important to screen lung function and popularize the knowledge of weight control in women with an early age at first childbirth.

Data Sharing Statement

Huizi Tian, Kai Kang, and Shixian Feng had full access to all of the data in the study and take responsibility for the integrity of the data.

Ethics Approval and Consent to Participate

All procedures in our study were in line with the Declaration of Helsinki. The study was approved by the ethics committees of the University of Oxford and the Chinese Center for Disease Control and Prevention (CDC). In addition, ethics approval was also obtained from the institutional research board at the Henan Provincial CDC and Huixian CDC. All participants provided written informed consent.

Acknowledgments

We thank the Chinese Center for Disease Control and Prevention, the Chinese Ministry of Health, the National Health and Family Planning Commission of China, and provincial/regional Health Administrative Departments. The most important acknowledgment is to the participants in the study and the members of the survey teams in Xinxiang City, Henan Province, as well as to the project development and management teams based in Beijing, Oxford.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or

critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by grants (2016YFC0900500, 2016YFC0900501) from the National Key Research and Development Program of China, grants from the Kadoorie Charitable Foundation in Hong Kong, and grants (202922/Z/16/Z, 088158/Z/09/Z, 104085/Z/14/Z) from Wellcome Trust in the UK.

Disclosure

The authors declare no conflicts of interest in this work.

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