

Title

Lower lung function associates with cessation of menstruation: UK Biobank data

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Low lung function associates with menopause, especially if it occurs early in life.

ABSTRACT

Little is known about the effect of cessation of menstruation on lung function. The aims of the study were to examine the association of lung function with natural and surgical cessation of menstruation, and assess whether lower lung function is associated with earlier age at cessation of menstruation.

The study was performed in 141,076 women from the UK Biobank, who had provided acceptable and reproducible spirometry measurements and information on menstrual status. The associations of lung function [FVC, FEV1, spirometric restriction (FVC<LLN), airflow obstruction (FEV1/FVC<LLN)] with cessation of menstruation and age at cessation of menstruation were assessed using regression analysis.

Women who had natural cessation of menstruation showed a lower FVC (-42mL; 95%CI -53, -30) and FEV1 (-34mL/s; 95%CI -43, -24) and higher risk of spirometric restriction (adjOR=1.27; 95%CI 1.18-1.37) than women still menstruating. These associations were stronger in women who had had a hysterectomy and/or oophorectomy. The earlier the natural cessation of menstruation, the lower the lung function. There was no clear association of lung function with age at hysterectomy and/or oophorectomy. Airflow obstruction was not associated with cessation of menstruation.

Lower lung function associates with cessation of menstruation, especially if it occurs early in life.

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INTRODUCTION

In adult men and women, low lung function is a major predictor of mortality, even in non-smokers and in those without symptoms of lung disease (1, 2). Although many authors have linked this to forced expiratory volume in 1 second (FEV1) and airflow obstruction, more recent work has shown that the strong association is between mortality and forced vital capacity (FVC), rather than airflow obstruction (1, 3). Multiple risk factors for low lung function have been put forward, including early life exposures, lifestyle factors (mainly smoking), environmental and occupational exposures, and the presence of asthma at any point during lifetime (4). These may operate by causing poor lung development in utero or during childhood, leading to failure to achieve maximal lung function early in life, or through more rapid decline in lung function with age during adulthood.

Differences in lung development and lung function between males and females are present throughout the life course and have been attributed to sex-specific responses to environmental or lifestyle insults and to effect of sex hormones (5, 6). Menopause, the cessation of menstruation, usually in response to a natural age-related decline in sex hormones commonly occurs between 45 and 55 years of age, although there is considerable variation (7, 8). Cessation of menstruation is sometimes precipitated by surgical interventions such as oophorectomy and hysterectomy. In young women, these interventions may prompt the prescription of hormone replacement therapy (HRT).

The cessation of menstruation has been examined in relation to several chronic diseases and health parameters, but little is known about its effect on lung function. Epidemiologic evidence on the association of menopause with lung function is limited, conflicting, inconclusive, and based largely on underpowered cross-sectional studies. In two studies with a combined total of less than 3300 women, the European Community Respiratory Health Survey II and the Mater University of Queensland Study of Pregnancy, menopause was

associated with both lower FEV1 and FVC (9, 10). In a smaller study, the Isparta Menopause and Health Study, menopause was associated with lower FEV1 and FVC, but this was explained by age, and it was not associated with airflow obstruction (11). In contrast, another cross-sectional study of just over 3700 women from the Health Survey for England, natural and surgical cessation of menstruation were associated with less airflow obstruction and natural menopause was associated with higher FEV1, although only in women aged 55 to 64 (12).

Most women undergo natural menopause, i.e. natural cessation of menstruation, around the age of 50 years (8), which means that with increasing life expectancy they will spend a large part of their lives in a postmenopausal state. Thus, it is important to expand our understanding of the impact that menopause and other types of cessation of menstruation have on the lung.

The aims of this study were to: 1) examine the association of lung function with natural and surgical cessation of menstruation in the population-based sample of the UK Biobank; and 2) assess whether lower lung function is associated with earlier age at natural menopause.

METHODS

Study participants

UK Biobank is a very large multi-centre population-based study, established to allow the identification and improved understanding of the genetic and non-genetic determinants of disease in middle-aged and elder adults (13). The 273,467 women who took part in the UK Biobank were assessed, between 2006 and 2010, in 22 centres across England, Wales, and Scotland located in areas with sufficient population aged 40 to 69 living within 10 miles (16.1 km) of the testing centre. During assessment, participants completed a touchscreen

questionnaire to provide information on their lifestyle, medical and family history, and underwent physical measurements, including spirometry.

The UK National Research Ethics Service Committee North West – Haydock approved the study, and electronic written consent from each participant was obtained.

Lung function outcomes

Lung function was assessed, in each centre, by nurses or healthcare technicians trained in spirometry following a standard protocol and using a Vitalograph Pneumotrac 6800 spirometer (Vitalograph Ltd., Buckingham, UK). Participants did not perform spirometry if they answered ‘yes’ or were unsure of the following: chest infection in the last month (i.e., influenza, bronchitis, severe cold, pneumonia); history of detached retina; heart attack or surgery to eyes, chest or abdomen in last three months; history of collapsed lung; pregnancy (first or third trimester); and currently on medication for tuberculosis. The aim was to record two acceptable blows from a maximum of three attempts. The spirometer software compared the acceptability of the first two blows and, if acceptable (defined as a $\leq 5\%$ difference in FVC and FEV1), indicated to the fieldworkers that the third blow was not required. Post-bronchodilator measurements were not performed. Analyses in this report were conducted using data from women who had provided at least two spirograms complying with the following criteria: 1) without cough; 2) back-extrapolated volume $<5\%$ FVC (or $<150\text{mL}$ if greater); 3) flow $<25\text{mL}$ in final 1s of forced expiratory time (FET); 4) both FEV1 and FVC reproducible; and 5) FET $\geq 6\text{s}$ on best curve (highest FEV1+FVC) (figure 1).

Outcome measures were: i) FVC; ii) FEV1; iii) spirometric restriction, defined as FVC $<$ lower limit of normal (LLN) for age and height, based on reference equations for Caucasians from the third US National Health and Nutrition Examination Survey (NHANES)

(14); and iv) airflow obstruction, defined as $FEV1/FVC < LLN$, based on the same reference population.

Menstrual status

Menstrual status was considered in six groups (regular menstruation; irregular menstruation; natural menopause; hysterectomy only; oophorectomy only; oophorectomy + hysterectomy) and their definition was based on a series of questions. Women who replied 'no' to the question "have you had your menopause (periods stopped)?" were also asked "how many days is your usual menstrual cycle?" If they provided a number to this question, they were classified as having 'regular menstruation' (median menstrual cycle length was 28 days, IQR 25-28). If they chose the option 'irregular cycle' they were classified as having 'irregular menstruation'.

Women were considered to have had 'natural menopause' if they replied 'yes' to the question on menopause and 'no' to both "have you had both ovaries removed?" (oophorectomy) and "have you had a hysterectomy (womb removed)?" (hysterectomy). Those whose ovaries and/or uterus were removed after their natural cessation of menstruation were classified as having had 'natural menopause'. Women were classified into three other groups depending on the type of surgical cessation of menstruation: 'hysterectomy only'; 'oophorectomy only'; and 'oophorectomy+hysterectomy'. Women unsure whether they had menopause were excluded from the analysis.

Statistical analysis

Following exclusions of women who had used an inhaler in the last hour prior to spirometry, women unsure whether they had menopause, those who were pregnant or reported a history of gynaecological cancer, and those who had reported an age at menopause less than 35 or greater than 65, the final sample for analysis comprised of 141,076 women.

The association of menstrual status with FVC and FEV1 was examined using linear regression. For the association with FVC<LLN and FEV1/FVC<LLN, logistic regression was used instead. Three models adjusting for potential confounders were used: Model 1, adjusted for recruitment centre, age (restricted cubic splines with five knots), ethnicity (White, non-White), standing height (continuous), and Townsend deprivation index (continuous); Model 2, further adjusted for reproductive characteristics [age at menarche (continuous), oral contraceptive ever use (yes, no), hormone replacement therapy (HRT) use (never, ex-user, current user), and number of live births (0, 1, 2, 3, 4, 5+)]; and Model 3, further adjusted for lifestyle-related characteristics [smoking status (lifetime non-smoker, ex-smoker, current smoker), pack-years (continuous), and body mass index (BMI; <18.5 kg/m², 18.5-24.99 kg/m², 25.00-29.99 kg/m², >29.99 kg/m²)]. In a sensitivity analysis, the associations of lung function with menstrual status were re-examined excluding women: 1) of non-White ethnicity; 2) with self-reported doctor-diagnosed asthma and/or chronic obstructive pulmonary disease (COPD); 3) who ever used HRT; 4) who ever smoked; and 5) those with an extreme BMI (<18.5 kg/m² or >29.99 kg/m²).

The association of lung function with natural menopause was further assessed by age group (age quintiles among women who had ceased menstruating) and according to age at menopause [<45 years (10%), 45-47 years (15%), 48-53 years (50%), 54-55 years (15%), 56+ years (10%)], with natural menopause between the age of 48 and 53 as reference. In order to examine whether surgical cessation of menstruation is worse than natural cessation, similar analyses were carried out for hysterectomy only and oophorectomy+hysterectomy among women who have never taken HRT. These analyses were not carried out for women who had had an oophorectomy only due to the small size of this group (n=214).

Results were considered statistically significant when *P* was less than 0.05. Statistical analysis was performed using Stata v.14 (StataCorp LP, College Station, TX).

RESULTS

Characteristics of the 141,076 women included in this study are shown in table 1. As compared to women with regular or irregular menstruation, women who had stopped menstruating were older, more likely to be ex-smokers, and less likely to have ever used a contraceptive pill. More than two thirds of the women who had had surgical cessation of menstruation were ex- or current users of HRT. Ever users of HRT were more likely to be ever smokers and heavier than those who have never taken HRT (supplementary table 1). The prevalence of spirometric restriction was higher in women who had stopped menstruating, while the prevalence of airflow obstruction was slightly higher in women still menstruating. Both FEV1 and FVC were lower in women who had stopped menstruating. Just over half of the women who had natural menopause reported their last menstruation to have occurred at an age between 48 and 53 years. Most women who had undergone surgical cessation of menstruation, had their surgical intervention before they were 48 years of age (supplementary figure 1).

Women excluded from the analyses due to low quality of spirometric data were similar to those included (supplementary table 2).

Association of lung function with natural cessation of menstruation

After full adjustment (model 3), women with irregular menstruation and natural menopause showed lower FVC [irregular menstruation: -17 mL (95%CI -31, -3); natural menopause: -42 mL (95%CI -53, -30)], lower FEV1 [irregular menstruation: -12 mL/s (95%CI -24, 0); natural menopause: -34 mL/s (95%CI -43, -24)] and higher risk of spirometric restriction [irregular menstruation: odds ratio (OR)=1.16 (95%CI 1.05-1.28); natural menopause (OR)=1.27 (95%CI 1.18-1.37)] than those still menstruating. There was no association of airflow obstruction with irregular menstruation or natural menopause (table 2).

Sensitivity analyses restricted to 33,406 white women, who have never smoked, have a BMI of 18.5-29.99 kg/m², do not have doctor-diagnosed asthma or COPD, and have never used HRT did not materially alter the results reported above (table 2; supplementary table 4).

Association of lung function with surgical cessation of menstruation

Women who had undergone hysterectomy, oophorectomy or both had lower FVC [hysterectomy only: -51 mL (95%CI -64, -37); oophorectomy only: -90 mL (95%CI -159, -20); oophorectomy+hysterectomy: -54 mL (95%CI -69, -39)], lower FEV1 [hysterectomy only: -32 mL/s (95%CI -43, -20); oophorectomy only: -46 mL/s (95%CI -105, 12); oophorectomy+hysterectomy: -33 mL/s (95%CI -46, -21)] and higher risk of spirometric restriction [hysterectomy only: OR=1.31 (95%CI 1.20-1.43), oophorectomy only: OR=1.69 (95%CI 1.14-2.50); oophorectomy+hysterectomy: OR=1.36 (95%CI 1.24-1.50)] than women who were menstruating regularly. These associations were present even after sensitivity analyses. Although there was some evidence that women who had hysterectomy with or without oophorectomy showed a lower risk of airflow obstruction, this observation was not seen after sensitivity analyses (table 2; supplementary table 4).

Effect of age at natural menopause and surgical cessation of menstruation on lung function

Among postmenopausal women, the earlier the natural menopause, the lower the FVC (and FEV1) and higher the risk of spirometric restriction (figures 2 and 3; supplementary tables 5-7). There was no clear association of airflow obstruction with age at natural menopause (figure 4; supplementary table 8) nor of lung function with age at surgical cessation of menstruation, i.e. hysterectomy only or oophorectomy+hysterectomy (supplementary tables 9-10).

DISCUSSION

In this population-based study of adult women, lower FVC and an increased risk of spirometric restriction were associated with natural and surgical cessation of menstruation, as compared with regular menstruation. The associations with natural menopause were stronger among women who ceased menstruating at an earlier age. These findings were unlikely to be confounded by smoking as they were observed in women who were lifetime non-smokers.

The strengths of our study are: 1) a very large sample size, which allows for more precise effect estimates; 2) the use of a standardised questionnaire for collection of data and protocol for spirometry across sites; 3) the use of spirometric measurements with the best quality only; and 4) the adjustment of models for a large set of confounders, including reproductive and lifestyle-related characteristics.

Our study also has limitations. As with all cross-sectional studies, we are unable to draw firm conclusions in terms of temporality. However, we think it is unlikely that low lung function leads to menopause. We are aware that women who smoke tend to have earlier menopause (15), and also low lung function, but as the study is of considerable size, we were able to restrict analyses to a large group of women who have never smoked and see that our findings were unaltered. Both lung function later in life and age at menopause have been associated with socioeconomic status in childhood (16, 17), but we do not have this information. We have adjusted for the Townsend deprivation index of place of residence at the time of assessment. Some women were unsure whether they were menopausal or not, and they were excluded from all analyses. It is difficult to predict how the inclusion of these women would affect our results, but since they were likely perimenopausal (median age: 51; IQR 48-53) and their median FVC (3.31 L) and FEV1 (2.57 L/s) were between those of women with

irregular menstruation (FVC: 3.45 L; FEV1: 2.70 L/s) and women who had undergone natural menopause (FVC: 3.02; FEV1: 2.30 L/s) it is unlikely that our findings would be different. Those who were included might have responded incorrectly regarding their menstrual status, but this is likely a non-differential misclassification error leading to underestimation of true effects rather than biased estimates. It is possible that women with worse lung function, and early menopause, have died younger, meaning that the associations between menopause and lung function in the older groups may be diluted even further. Endometriosis, an indication for oophorectomy without hysterectomy in young women, has been associated with asthma, but this condition was rare (<2.5%) in women who had both ovaries removed. At the assessment centres, spirometry testing did not follow the ATS/ERS recommendation of performing at least three manoeuvres to measure FVC and FEV1, but we have used only spirometric data that fulfilled all other between- and within-manoeuve criteria (18). Because we used pre-bronchodilator instead of post-bronchodilator spirometry, we were unable to distinguish COPD from asthma based on lung function. However, the association of airflow obstruction with cessation of menstruation was null. Some could argue that our results may be dependent on the reference equations we used (NHANES), but we obtained very similar results using the Global Lungs Initiative equations (19) (data not shown).

To date, this is by far the largest population-based study to assess the association between lung function and menstrual status. The inverse association of FVC and FEV1 with natural menopause is consistent with two previous reports. Real et al. studied 1274 women from Europe and the USA and reported much lower FVC and FEV1 in women who had stopped menstruating for at least six months, as compared to women with regular menstruation (9). In an Australian study with 2020 women, Hayatbakhsh et al. reported a lower FVC and FEV1 in

postmenopausal women as opposed to premenopausal women (10). These studies reported much larger differences in FVC (Real et al.: -115 mL; Hayatbakhsh et al.: -60 mL) and FEV1 (Real et al.: -120 mL/s; Hayatbakhsh et al.: -80 mL/s), but their studies were smaller and their analyses were adjusted for considerably less confounders. In contrast, Songur et al. studied 1070 Turkish women and reported no difference in FVC or FEV1 between pre- and postmenopausal women (11). Like Real et al. (9), they also showed no association of menopause with airflow obstruction. In an English study with 3724 women, Jarvis and Leynaert reported less airflow obstruction in women who had either natural or surgical cessation of menstruation, as compared to menstruating women, but they only observed this amongst those aged 55 to 64 years (12). We observed less airflow obstruction in women who have undergone surgical cessation of menstruation, but this may have been due to use of HRT since exclusion of women who had used this therapy made the association disappear. This finding is supported by at least a population-based observational study and two trials showing better lung function (FVC and FEV1) in postmenopausal women taking HRT (20-22). None of these studies assessed the association of cessation of menstruation with spirometric restriction. Previous studies have also not examined the effect of different ages at natural menopause, or surgical cessation of menstruation, on lung function.

The biological mechanisms underlying the association of a lower lung function with cessation of menstruation are not fully understood, but may be related to changes in the levels of circulating sex hormones and increased insulin resistance (23). It has been speculated that with cessation of menstruation the female body may reduce its capacity to detoxify, potentiating the bioaccumulation of chemicals, such as those found in cigarette smoke (24), to levels that could have adverse effects on the lungs. Accelerated bone mass loss (25) and weakened ligaments, which commonly follow the cessation of menstruation, could eventually

lead to compression and/or fracture of the vertebrae (26) and/or slippage of the ribs, constricting the lungs and reducing their volume, hence increasing the risk of restrictive lung condition. Medical interventions to treat osteoporotic vertebral compression fractures have been shown to lead to an increase in the FVC (27, 28). Another explanation for worse lung function in women who had an early cessation of menstruation may reside on ‘biological aging’. Some studies have shown lower FVC and FEV1 in those with shorter leukocyte telomeres (a marker of faster biological aging) (29, 30), which in turn have been suggested to be a marker of early menopause (31).

In summary, lower lung function, particularly lower FVC, associates with cessation of menstruation. Although more research on this topic is needed and longitudinal studies would be welcome, our findings, together with evidence that low lung function and an early age at menopause have both been associated with increased mortality (3, 32), should alert clinicians to the risk of poor lung function in postmenopausal women, especially in those who have an early cessation of menstruation.

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CONFLICT OF INTEREST

None to declare.

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The funder of this study had no role in study design, data analysis and interpretation of results, or writing of the manuscript.

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Table 1. Characteristics of women in UK Biobank included in this study.

	Regular menstruation	Irregular menstruation	Natural menopause	Surgical interventions before menopause			Total population
				Hysterectomy only	Oophorectomy only	Oophorectomy + hysterectomy	
N	29,249	6,058	83,023	12,551	214	9,981	141,076
Age (years), median (IQR)	45 (43-49)	48 (45-51)	60 (56-64)	61 (55-64)	57 (51-63)	61 (55-64)	58 (50-63)
Age at menarche (years), median (IQR)‡	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)
Age at cessation of menstruation (years), median (IQR)*	-	-	51 (48-53)	41 (38-45)	44 (37-50)	46 (41-50)	-
Ethnicity (%)							
White	92.4	95.3	96.3	96.0	92.1	95.6	95.8
Non-White	7.6	4.7	3.7	4.0	7.9	4.4	4.2
Standing height (cm), median (IQR)**	164 (160-168)	164 (160-168)	162 (158-166)	162 (158-166)	161 (158-166)	162 (157-166)	162 (158-167)
BMI (kg/m ²), median (IQR)***	25.3 (22.8-28.8)	25.7 (23.0-29.6)	26.0 (23.5-29.3)	27.1 (24.4-30.7)	26.0 (23.7-30.3)	27.2 (24.3-30.9)	26.0 (23.4-29.5)
Oral contraceptive (ever) use (%)†	89.2	92.2	79.3	80.3	78.9	78.9	82.0
Hormone replacement therapy (%)π							
Never used	96.7	95.5	55.3	39.7	51.6	14.8	61.3
Ex-user	1.9	3.2	39.6	49.2	40.4	64.6	32.9
Current user	1.4	1.3	5.1	11.1	8.0	20.6	5.8
Live births (%)÷							
0	25.4	25.3	16.2	10.4	22.0	15.4	17.9
1-2	55.1	55.9	58.8	59.3	49.5	58.0	58.0
3-4	18.4	17.7	23.5	28.2	26.2	24.9	22.7
5+	1.1	1.1	1.5	2.1	2.3	1.7	1.4
Smoking status (%)****							
Lifetime non-smoker	64.5	64.7	58.2	57.8	55.4	57.3	59.7
Ex-smoker	25.4	25.6	33.9	33.0	34.6	33.3	31.6
Current smoker	10.1	9.7	7.9	9.2	10.0	9.4	8.7
Pack-years , median (IQR)¥	12.8 (6.8-21.0)	13.0 (6.5-22.0)	18.0 (9.0-30.0)	19.0 (10.0-30.8)	22.0 (10.5-30.0)	19.5 (10.0-31.7)	16.5 (8.5-28.0)
Townsend deprivation index , median (IQR)€	-1.9 (-3.5, 0.8)	-2.2 (-3.6, 0.4)	-2.3 (-3.7, 0.0)	-2.3 (-3.7, 0.2)	-2.1 (-3.7, 0.7)	-2.3 (-3.7, 0.3)	-2.2 (-3.7, 0.2)
FVC (L), median (IQR)	3.51 (3.14-3.91)	3.45 (3.09-3.84)	3.02 (2.66-3.40)	3.01 (2.64-3.40)	3.02 (2.60-3.44)	2.98 (2.62-3.37)	3.13 (2.74-3.55)
FVC %predicted , median (IQR)	96.1 (87.6-104.7)	95.6 (86.6-104.2)	93.5 (84.2-102.7)	92.7 (83.5-102.0)	91.8 (81.1-101.6)	92.5 (83.0-101.7)	94.0 (84.8-103.1)
FEV1 (L/s), median (IQR)	2.75 (2.44-3.05)	2.70 (2.40-3.00)	2.30 (2.00-2.61)	2.30 (2.00-2.61)	2.32 (1.97-2.67)	2.28 (1.98-2.59)	2.40 (2.08-2.74)
FEV1 %predicted , median (IQR)	93.9 (84.9-102.6)	93.6 (84.5-102.4)	92.2 (81.9-101.9)	91.7 (81.6-101.5)	92.1 (79.5-101.8)	91.4 (81.2-101.3)	92.5 (82.5-102.0)
FVC < LLN (%)	12.3	13.3	15.5	16.9	22.4	17.6	15.0
FEV1/FVC < LLN (%)	8.9	8.0	8.7	7.4	4.7	7.9	8.6
Doctor-diagnosed asthma (%)	13.1	13.6	11.4	14.5	13.6	13.9	12.3
Wheeze in last year (%)	16.6	16.7	17.1	22.2	24.6	21.6	17.8
Doctor-diagnosed COPD (%)	0.03	0.02	0.31	0.49	0.47	0.30	0.26

IQR, interquartile range. ₺3,898 missing (regular: 832; irregular: 230; natural: 2,276; hysterectomy only: 277; oophorectomy only: 9; oophorectomy + hysterectomy: 274). *5,258 missing (natural: 4,686; hysterectomy only: 297; oophorectomy only: 27; oophorectomy + hysterectomy: 248). **81 missing (regular: 12; irregular: 1; natural: 47; hysterectomy only: 8; oophorectomy + hysterectomy: 13). ***1,765 missing (regular: 273; irregular: 75; natural: 1,065; hysterectomy only: 189; oophorectomy only: 6; oophorectomy + hysterectomy: 157). †289 missing (regular: 62; irregular: 9; natural: 154; hysterectomy only: 30; oophorectomy only: 1; oophorectomy + hysterectomy: 33). ‡303 missing (regular: 77; irregular: 16; natural: 159; hysterectomy only: 27; oophorectomy only: 1; oophorectomy + hysterectomy: 23). ÷74 missing (regular: 13; irregular: 1; natural: 44; hysterectomy only: 10; oophorectomy + hysterectomy: 6). ****2,611 missing (regular: 435; irregular: 101; natural: 1,605; hysterectomy only: 263; oophorectomy only: 3; oophorectomy + hysterectomy: 204). ¥17,129 missing (natural: 3,576; irregular: 707; natural: 10,153; hysterectomy only: 1,514; oophorectomy only: 29; oophorectomy + hysterectomy: 1,150). €163 missing (regular: 49; irregular: 9; natural: 80; hysterectomy only: 15; oophorectomy + hysterectomy: 10).

Table 2. Association of lung function with menstrual status.

		FVC (mL)	FEV1 (mL/s)	FVC < LLN	FEV1/FVC < LLN
	N	Difference (95% CI)	Difference (95% CI)	OR (95% CI)	OR (95% CI)
Main analysis (N = 115,848)					
Menstrual status					
Regular menstruation	24,135	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	4,959	-17 (-31, -3)	-12 (-24, 0)	1.16 (1.05-1.28)	0.95 (0.85-1.06)
Natural menopause	68,068	-42 (-53, -30)	-34 (-43, -24)	1.27 (1.18-1.37)	1.03 (0.94-1.13)
Hysterectomy only	10,300	-51 (-64, -37)	-32 (-43, -20)	1.31 (1.20-1.43)	0.86 (0.77-0.96)
Oophorectomy only	168	-90 (-159, -20)	-46 (-105, 12)	1.69 (1.14-2.50)	0.64 (0.33-1.23)
Oophorectomy + hysterectomy	8,218	-54 (-69, -39)	-33 (-46, -21)	1.36 (1.24-1.50)	0.87 (0.77-0.98)
Sensitivity analysis* (N = 33,406)					
Menstrual status					
Regular menstruation	11,131	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	2,261	-29 (-50, -8)	-21 (-38, -4)	1.19 (1.00-1.40)	0.93 (0.77-1.14)
Natural menopause	17,910	-38 (-58, -19)	-27 (-43, -10)	1.32 (1.13-1.54)	0.97 (0.80-1.18)
Hysterectomy only	1,621	-61 (-88, -34)	-42 (-64, -20)	1.28 (1.04-1.58)	0.97 (0.74-1.28)
Oophorectomy only	32	-118 (-277, 40)	-52 (-182, 78)	1.23 (0.37-4.10)	0.53 (0.07-3.93)
Oophorectomy + hysterectomy	451	-60 (-106, -14)	-34 (-71, 4)	1.28 (0.91-1.80)	1.05 (0.66-1.66)

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, hormone replacement therapy use, number of live births, smoking status, pack-years, and body mass index. *Among White women, who have never smoked, have a body mass index of 18.5-29.99 kg/m², do not have doctor-diagnosed asthma or chronic obstructive pulmonary disease (COPD), and have never used hormone replacement therapy.

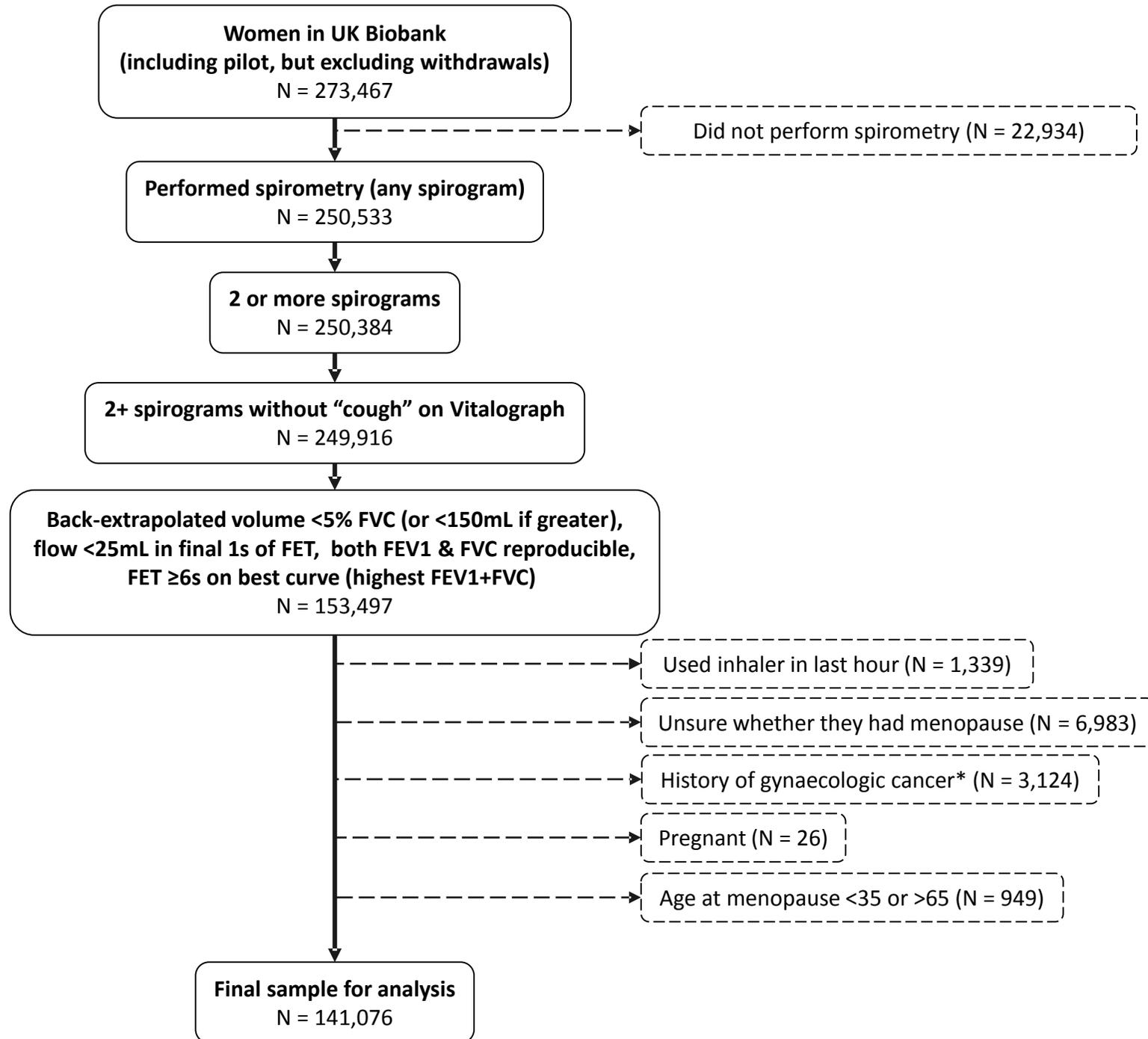
Figures' legends

Figure 1. Selection of participants in the study. *At least one of female genital tract cancer; ovarian cancer; uterine/endometrial cancer; cervical cancer; vaginal cancer; vulval cancer; CIN/pre-cancer cells cervix; fallopian tube cancer.

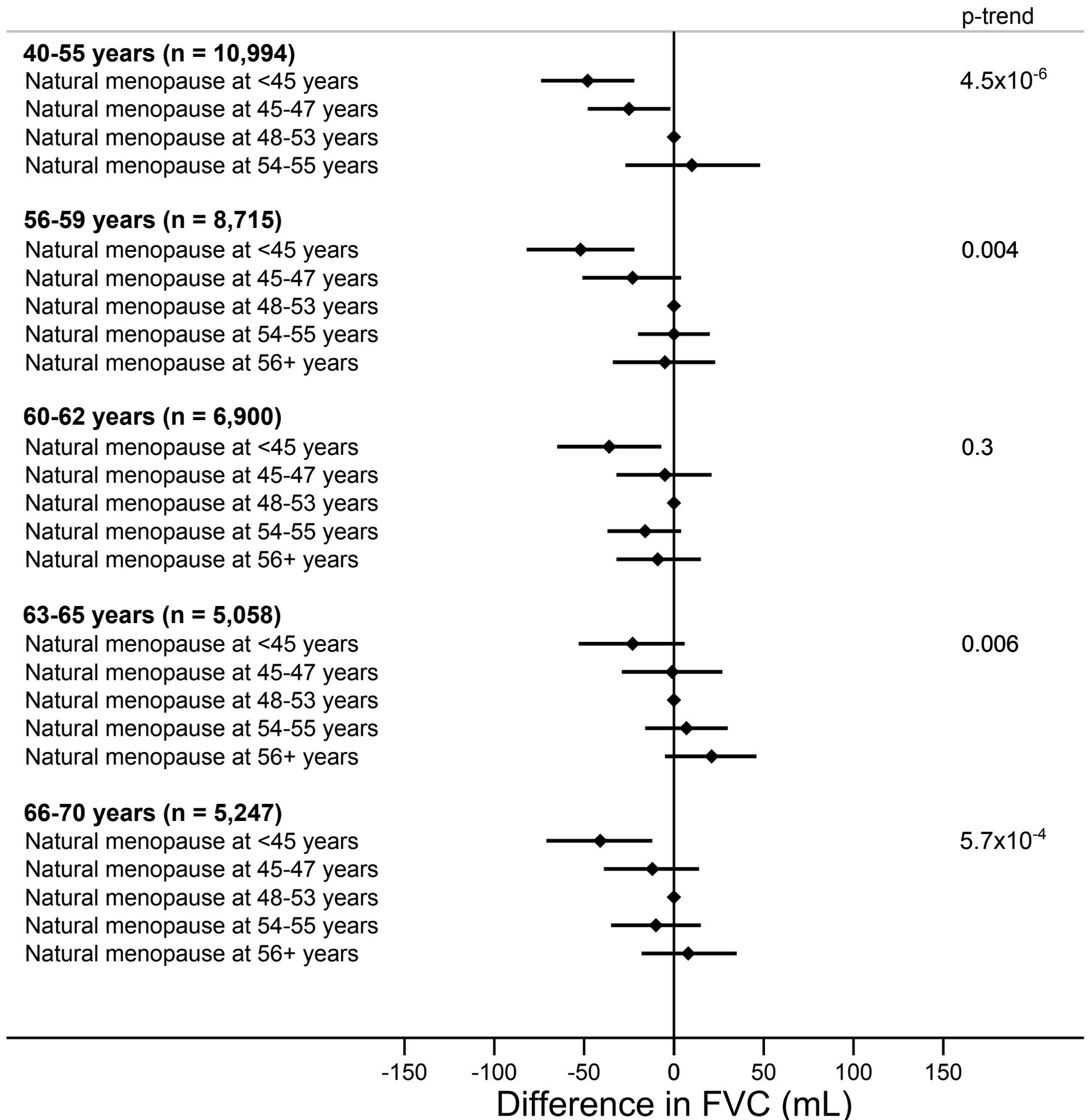
Figure 2. Association of FVC (mL) with age at natural menopause, by age group. Reference group is women who had menopause at 48-53 years.

Figure 3. Association of spirometric restriction ($FVC < LLN$) with age at natural menopause, by age group. Reference group is women who had menopause at 48-53 years.

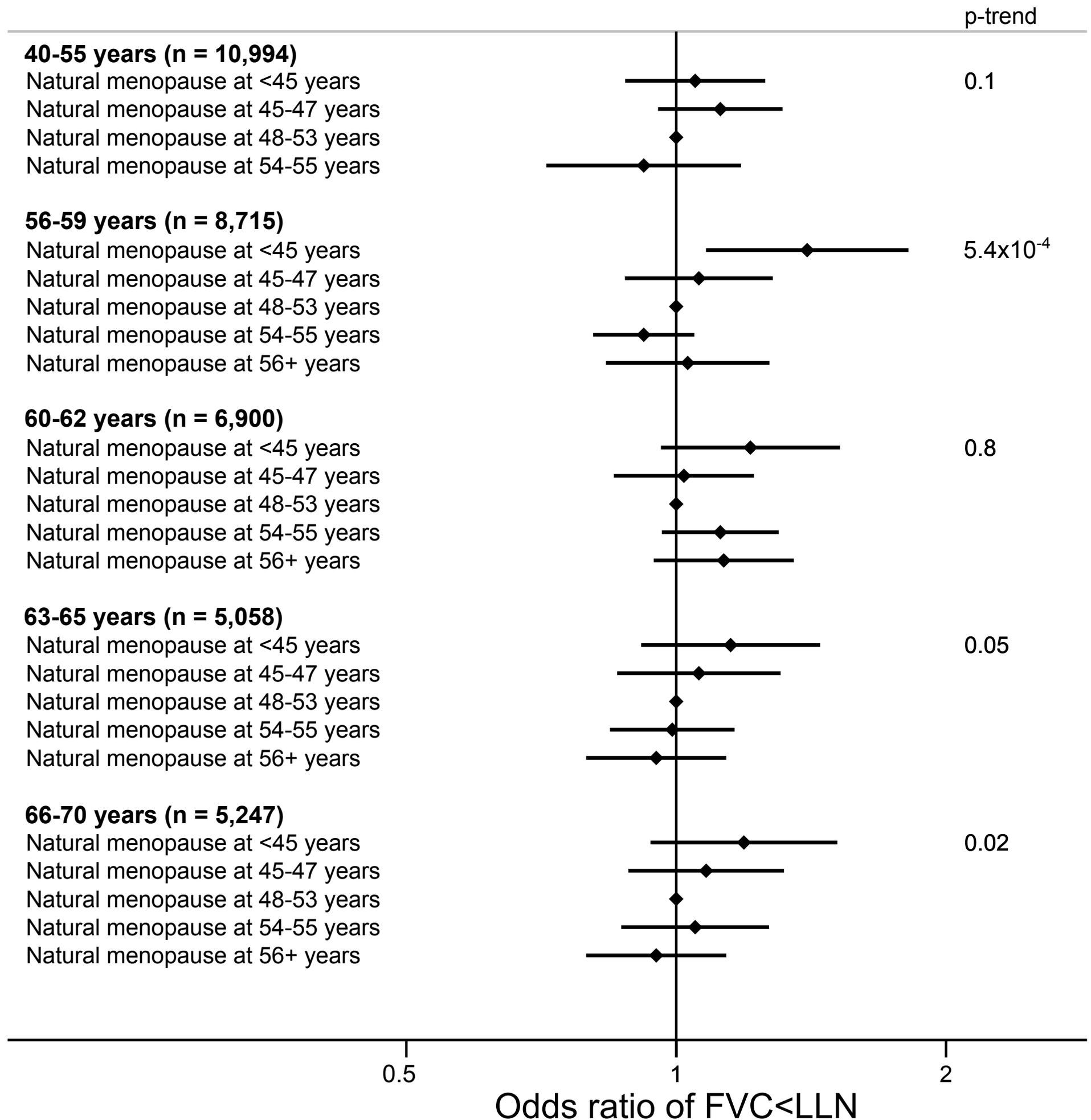
Figure 4. Association of airflow obstruction ($FEV1/FVC < LLN$) with age at natural menopause, by age group. Reference group is women who had menopause at 48-53 years.



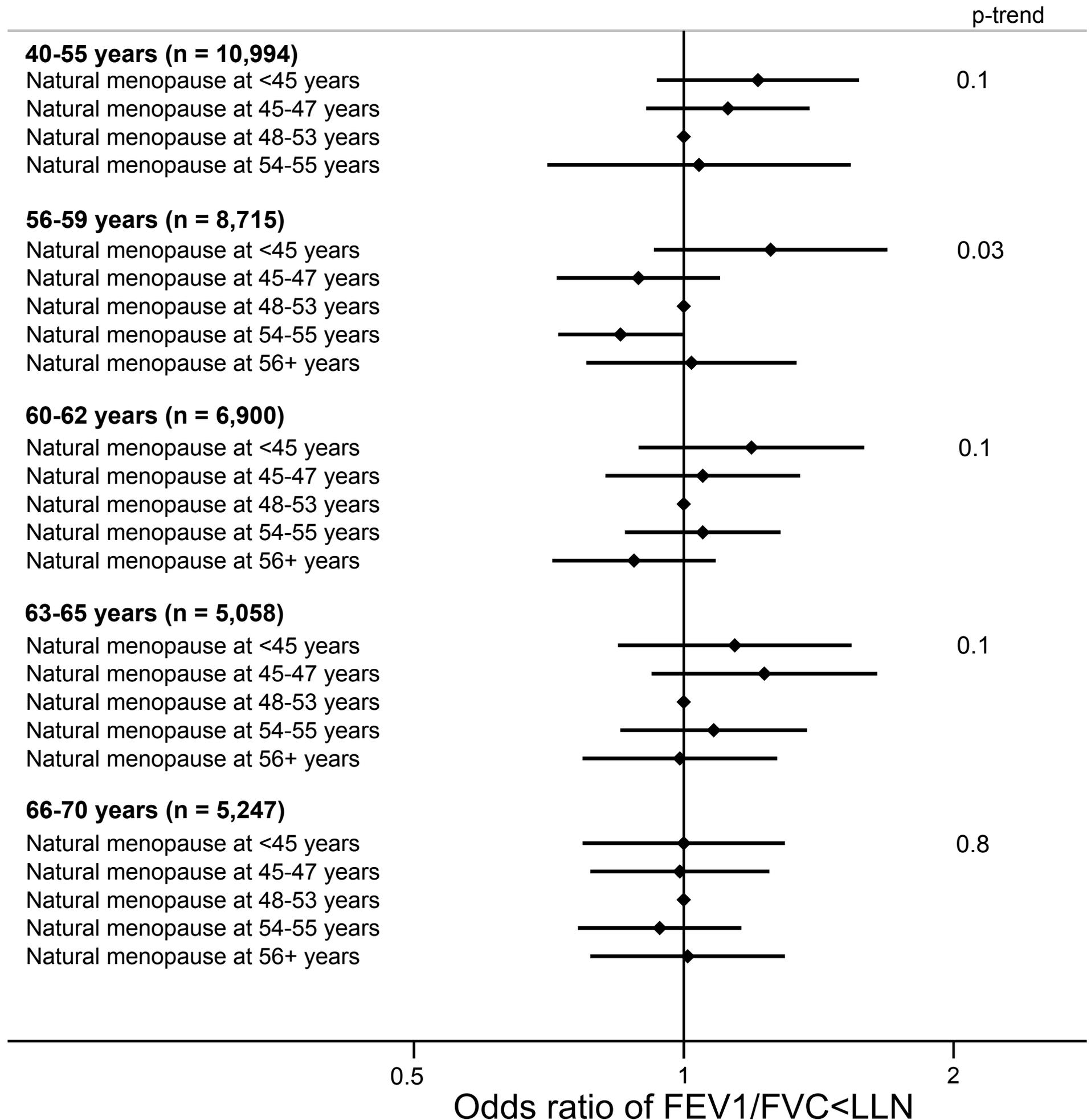
Association of age at natural menopause with FVC, by age group



Association of age at natural menopause with FVC<LLN, by age group



Association of age at natural menopause with FEV1/FVC<LLN, by age group



Online Supplement

Title

Lower lung function associates with cessation of menstruation: UK Biobank data

Authors

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- Supplementary table 1** shows that ever users of hormonal replacement therapy (HRT) were more likely to be ever smokers and heavier than those who have never taken HRT.
- Supplementary table 2** summarizes the characteristics of women from UK Biobank excluded from this study due to low quality of spirometry, and shows that these women were similar to those included in this analyses.
- Supplementary table 3** shows how the differences in lung function between women who had undergone either natural or surgical cessation of menstruation and women still menstruating are explained by demographic (model 1), plus reproductive (model 2), and lifestyle-related characteristics (model 3).
- Supplementary table 4** shows that our main findings are unlikely to be confounded by ethnicity, smoking status, body mass index (BMI), asthma, COPD, or use of HRT. The exception to this is the association of airflow obstruction (FEV1/FVC<LLN) with hysterectomy with or without oophorectomy which seems to be explained by smoking, BMI, and use of HRT.
- Supplementary table 5** shows that among postmenopausal women, the earlier they underwent natural menopause, the lower their FVC. This finding is unlikely to be affected by HRT, smoking or BMI.
- Supplementary table 6** shows that among postmenopausal women, the earlier they underwent natural menopause, the lower their FEV1. This finding is unlikely to be affected by HRT, smoking or BMI.
- Supplementary table 7** shows that among postmenopausal women, the earlier they underwent natural menopause, the higher their risk of spirometric restriction (FVC<LLN). This finding is unlikely to be affected by HRT, smoking or BMI.
- Supplementary table 8** shows that among postmenopausal women there was no clear association of airflow obstruction with age at natural menopause. This finding is unlikely to be affected by HRT, smoking or BMI.
- Supplementary table 9** shows that among women who had hysterectomy, and never used HRT, there was no clear association of lung function (FVC, FEV1, FVC<LLN, FEV1/FVC<LLN) with age at hysterectomy.
- Supplementary table 10** shows that among women who had oophorectomy+hysterectomy, and never used HRT, there was no clear association of lung function (FVC, FEV1, FVC<LLN, FEV1/FVC<LLN) with age at oophorectomy+hysterectomy.

Supplementary table 1. Distribution of body mass index and smoking status according to hormonal replacement therapy status.

	HRT	
	Never users	Ever users
BMI (kg/m²), median (IQR)*	25.8 (23.2-29.4)	26.3 (23.8-29.6)
BMI (kg/m²), (%)*		
<18.5	0.6	0.4
18.5-24.99	41.4	35.9
25.00-29.99	35.8	40.4
30+	22.2	23.3
Smoking status (%)**		
Lifetime non-smoker	63.3	53.9
Ex-smoker	28.1	37.3
Current smoker	8.6	8.8

IQR, interquartile range. *1,765 missing. **2,611 missing.

Supplementary table 2. Characteristics of women in UK Biobank excluded from this study (with at least two spirograms without cough and back-extrapolated volume <5% FVC (or <150mL if greater), but excluding those with FET ≥6s on best curve (highest FEV1 + FVC)). Women who: 1) used inhaler in the last hour; 2) were unsure whether they had menopause; 3) were pregnant; 4) had gynaecologic cancer; and 5) reported an age at menopause <35 or >65 are not included.

	Regular menstruation	Irregular menstruation	Natural menopause	Surgical interventions before menopause			Total population
				Hysterectomy only	Oophorectomy only	Oophorectomy + hysterectomy	
N	18,381	3,728	47,152	7,126	142	5,710	82,239
Age (years), median (IQR)	45 (43-48)	47 (44-50)	61 (56-64)	60 (55-65)	57 (50-62)	61 (55-65)	57 (49-63)
Age at menarche (years), median (IQR)‡	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)	13 (12-14)
Age at cessation of menstruation (years), median (IQR)*	-	-	50 (48-53)	41 (37-45)	42 (37-50)	45 (40-50)	-
Ethnicity (%)							
White	89.5	93.1	94.6	93.7	86.6	93.2	93.2
Non-White	10.5	6.9	5.4	6.3	13.4	6.8	6.8
Standing height (cm), median (IQR)**	164 (160-169)	164 (160-169)	162 (158-166)	162 (158-166)	161 (158-166)	162 (158-166)	163 (158-167)
BMI (kg/m ²), median (IQR)***	25.0 (22.4-28.6)	25.3 (22.7-29.2)	26.1 (23.5-29.6)	27.2 (24.4-30.8)	27.2 (24.0-31.1)	27.4 (24.5-31.1)	26.0 (23.3-29.6)
Oral contraceptive (ever) use (%)†	87.1	89.7	76.9	77.9	73.9	76.2	79.8
Hormone replacement therapy (%)π							
Never used	96.9	96.0	57.4	42.4	53.9	16.7	63.9
Ex-user	1.9	2.7	37.9	47.6	37.6	63.9	30.9
Current user	1.2	1.3	4.7	10.0	8.5	19.4	5.2
Live births (%)÷							
0	27.0	25.5	17.8	11.7	19.7	16.5	19.6
1-2	54.0	55.7	57.6	57.6	57.8	57.2	56.7
3-4	17.7	18.0	22.8	28.4	21.1	24.1	22.0
5+	1.3	0.8	1.7	2.4	1.4	2.2	1.7
Smoking status (%)****							
Lifetime non-smoker	69.1	69.7	63.3	63.7	69.3	63.8	64.9
Ex-smoker	21.3	21.3	29.1	28.2	17.1	27.8	26.8
Current smoker	9.6	9.0	7.6	8.1	13.6	8.4	8.3
Pack-years , median (IQR)¥	12.2 (6.8-20.2)	13.0 (7.0-21.9)	18.0 (9.0-30.0)	19.5 (9.8-30.8)	22.0 (10.8-33.9)	19.5 (10.0-31.3)	16.5 (8.5-28.0)
Townsend deprivation index , median (IQR) €	-1.8 (-3.5, 1.0)	-2.05 (-3.6, 0.6)	-2.2 (-3.7, 0.3)	-2.2 (-3.7, 0.3)	-1.0 (-3.3, 1.9)	-2.1 (-3.6, 0.6)	-2.1 (-3.6, 0.5)
FVC (L), median (IQR)	3.54 (3.11-3.99)	3.49 (3.09-3.92)	3.05 (2.65-3.48)	3.04 (2.62-3.48)	3.06 (2.57-3.55)	3.00 (2.58-3.43)	3.17 (2.73-3.63)
FVC %predicted , median (IQR)	96.1 (86.1-105.7)	95.7 (86.3-105.2)	94.0 (83.5-104.6)	93.3 (82.3-104.0)	91.0 (80.2-102.7)	92.3 (81.7-102.9)	94.4 (84.0-104.7)
FEV1 (L/s), median (IQR)	2.78 (2.43-3.11)	2.74 (2.42-3.08)	2.32 (2.00-2.65)	2.33 (1.99-2.66)	2.33 (1.81-2.73)	2.30 (1.96-2.62)	2.43 (2.08-2.80)
FEV1 %predicted , median (IQR)	94.1 (84.2-103.6)	94.7 (84.7-104.2)	92.8 (81.7-103.2)	92.4 (80.9-102.7)	89.2 (73.1-100.8)	91.4 (80.6-102.0)	93.0 (82.3-103.2)
FVC < LLN (%)	15.8	15.4	17.8	20.0	22.5	21.2	17.7
FEV1/FVC < LLN (%)	13.1	10.8	13.1	12.2	16.2	12.0	12.8
Doctor-diagnosed asthma (%)	10.6	11.0	8.8	12.1	12.9	12.0	9.8
Wheeze in last year (%)	14.9	15.4	15.2	20.0	30.7	20.0	15.9
Doctor-diagnosed COPD (%)	0.04	0.05	0.19	0.25	0.70	0.30	0.16

IQR, interquartile range. ₺2,613 missing (regular: 595; irregular: 140; natural: 1,484; hysterectomy only: 174; oophorectomy only: 2; oophorectomy + hysterectomy: 218). *3,324 missing (natural: 2,897; hysterectomy only: 214; oophorectomy only: 26; oophorectomy + hysterectomy: 187). **93 missing (regular: 16; irregular: 5; natural: 55; hysterectomy only: 8; oophorectomy + hysterectomy: 9). ***1,214 missing (regular: 231; irregular: 49; natural: 741; hysterectomy only: 100; oophorectomy only: 4; oophorectomy + hysterectomy: 89). †259 missing (regular: 71; irregular: 15; natural: 134; hysterectomy only: 12; oophorectomy + hysterectomy: 27). ‡327 missing (regular: 86; irregular: 17; natural: 168; hysterectomy only: 32; oophorectomy only: 1; oophorectomy + hysterectomy: 23). †88 missing (regular: 22; irregular: 1; natural: 55; hysterectomy only: 5; oophorectomy + hysterectomy: 5). ****1,552 missing (regular: 277; irregular: 51; natural: 972; hysterectomy only: 150; oophorectomy only: 2; oophorectomy + hysterectomy: 100). ¥10,857 missing (natural: 2,357; irregular: 433; natural: 6,382; hysterectomy only: 898; oophorectomy only: 17; oophorectomy + hysterectomy: 770). €95 missing (regular: 24; irregular: 5; natural: 57; hysterectomy only: 3; oophorectomy + hysterectomy: 6).

Supplementary table 3. Association of lung function with menstrual status.

	Unadjusted (N = 141,076)	Model 1 (N = 140,833)	Model 2 (N = 136,388)	Model 3 (N = 115,848)
	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
FVC (mL)				
Regular menstruation	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	-53 (-69, -37)	-29 (-42, -16)	-28 (-41, -15)	-17 (-31, -3)
Natural menopause	-483 (-491, -475)	-51 (-62, -41)	-50 (-61, -39)	-42 (-53, -30)
Hysterectomy only	-493 (-505, -480)	-75 (-88, -63)	-76 (-89, -64)	-51 (-64, -37)
Oophorectomy only	-499 (-578, -421)	-115 (-178, -51)	-120 (-185, -55)	-90 (-159, -20)
Oophorect. + hysterect.	-519 (-532, -505)	-86 (-99, -73)	-86 (-100, -72)	-54 (-69, -39)
FEV1 (mL/s)				
Regular menstruation	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	-45 (-58, -31)	-18 (-30, -7)	-19 (-30, -7)	-12 (-24, 0)
Natural menopause	-441 (-448, -435)	-47 (-56, -38)	-45 (-54, -36)	-34 (-43, -24)
Hysterectomy only	-434 (-444, -424)	-53 (-64, -43)	-51 (-62, -41)	-32 (-43, -20)
Oophorectomy only	-409 (-473, -345)	-65 (-119, -12)	-66 (-121, -12)	-46 (-105, 12)
Oophorect. + hysterect.	-456 (-467, -445)	-63 (-74, -52)	-57 (-69, -45)	-33 (-46, -21)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
FVC < LLN				
Regular menstruation	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	1.10 (1.01-1.19)	1.20 (1.10-1.31)	1.19 (1.09-1.30)	1.16 (1.05-1.28)
Natural menopause	1.30 (1.25-1.36)	1.33 (1.25-1.42)	1.33 (1.24-1.42)	1.27 (1.18-1.37)
Hysterectomy only	1.44 (1.36-1.53)	1.46 (1.35-1.58)	1.47 (1.36-1.60)	1.31 (1.20-1.43)
Oophorectomy only	2.06 (1.49-2.84)	1.93 (1.37-2.71)	2.01 (1.42-2.84)	1.69 (1.14-2.50)
Oophorect. + hysterect.	1.52 (1.43-1.62)	1.54 (1.42-1.67)	1.57 (1.44-1.71)	1.36 (1.24-1.50)
FEV1/FVC < LLN				
Regular menstruation	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	0.89 (0.80-0.98)	0.94 (0.84-1.04)	0.95 (0.85-1.05)	0.95 (0.85-1.06)
Natural menopause	0.97 (0.93-1.02)	1.15 (1.06-1.25)	1.14 (1.04-1.23)	1.03 (0.94-1.13)
Hysterectomy only	0.82 (0.76-0.89)	0.94 (0.85-1.03)	0.90 (0.82-1.00)	0.86 (0.77-0.96)
Oophorectomy only	0.50 (0.26-0.94)	0.56 (0.30-1.07)	0.58 (0.31-1.11)	0.64 (0.33-1.23)
Oophorect. + hysterect.	0.87 (0.80-0.95)	1.00 (0.90-1.11)	0.93 (0.84-1.04)	0.87 (0.77-0.98)

Model 1: Adjusted for centre, age, ethnicity, standing height, and Townsend deprivation index. Model 2: Model 1 plus age at menarche, oral contraceptive use, hormone replacement therapy use, and number of live births. Model 3: Model 2 plus smoking status, pack-years, and body mass index.

Supplementary table 4. Association of lung function with menstrual status, after sensitivity analysis.

	White ethnicity (N = 110,475)	Lifetime non-smoker (N = 78,739)	18.5 to 29.99 kg/m ² (N = 88,555)	Without asthma/COPD (N = 101,519)	Never used HRT (N = 71,397)	White ethnicity + lifetime non-smoker + 18.5 to 29.99 kg/m ² + without asthma/COPD + never used HRT (N = 33,406)
	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)	Difference (95% CI)
FVC (mL)						
Regular menstruation	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	-22 (-36, -7)	-20 (-37, -4)	-15 (-31, 1)	-18 (-33, -3)	-19 (-34, -5)	-29 (-50, -8)
Natural menopause	-41 (-52, -29)	-40 (-54, -27)	-45 (-58, -32)	-39 (-51, -27)	-42 (-55, -29)	-38 (-58, -19)
Hysterectomy only	-49 (-63, -35)	-49 (-65, -32)	-55 (-71, -39)	-49 (-63, -34)	-58 (-75, -40)	-61 (-88, -34)
Oophorectomy only	-101 (-173, -28)	-75 (-163, 12)	-109 (-191, -26)	-74 (-148, 0)	-136 (-234, -38)	-118 (-277, 40)
Oophorect. + hysterect.	-52 (-67, -36)	-50 (-68, -32)	-57 (-74, -39)	-54 (-70, -38)	-59 (-87, -30)	-60 (-106, -14)
FEV1 (mL/s)						
Regular menstruation	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	-16 (-29, -4)	-13 (-27, 1)	-11 (-25, 2)	-12 (-24, 1)	-14 (-26, -2)	-21 (-38, -4)
Natural menopause	-32 (-42, -22)	-29 (-40, -17)	-37 (-48, -26)	-32 (-42, -22)	-36 (-48, -25)	-27 (-43, -10)
Hysterectomy only	-31 (-42, -19)	-27 (-41, -13)	-36 (-49, -22)	-31 (-43, -19)	-44 (-58, -29)	-42 (-64, -20)
Oophorectomy only	-55 (-116, -19)	-37 (-110, 36)	-52 (-122, 17)	-32 (-94, 29)	-68 (-150, 15)	-52 (-182, 78)
Oophorect. + hysterect.	-31 (-44, -18)	-28 (-43, -13)	-36 (-51, -22)	-35 (-48, -22)	-38 (-62, -13)	-34 (-71, 4)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
FVC < LLN (NHANES III)						
Regular menstruation	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	1.21 (1.09-1.33)	1.13 (1.01-1.27)	1.15 (1.03-1.30)	1.17 (1.05-1.30)	1.17 (1.06-1.29)	1.19 (1.00-1.40)
Natural menopause	1.27 (1.17-1.38)	1.24 (1.14-1.36)	1.33 (1.21-1.46)	1.27 (1.17-1.38)	1.27 (1.17-1.39)	1.32 (1.13-1.54)
Hysterectomy only	1.31 (1.19-1.44)	1.24 (1.11-1.38)	1.35 (1.21-1.50)	1.28 (1.16-1.41)	1.33 (1.20-1.49)	1.28 (1.04-1.58)
Oophorectomy only	1.84 (1.22-2.77)	1.23 (0.72-2.12)	1.96 (1.22-3.14)	1.61 (1.04-2.50)	1.74 (1.01-2.99)	1.23 (0.37-4.10)
Oophorect. + hysterect.	1.36 (1.23, 1.50)	1.29 (1.14-1.45)	1.41 (1.25-1.59)	1.39 (1.25-1.54)	1.34 (1.13-1.58)	1.28 (0.91-1.80)
FEV1/FVC < LLN (NHANES III)						
Regular menstruation	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Irregular menstruation	0.96 (0.85-1.08)	0.94 (0.81-1.08)	0.96 (0.85-1.09)	0.93 (0.80-1.07)	0.95 (0.85-1.07)	0.93 (0.77-1.14)
Natural menopause	1.02 (0.93-1.13)	1.01 (0.90-1.14)	1.06 (0.96-1.17)	1.03 (0.92-1.15)	1.04 (0.93-1.15)	0.97 (0.80-1.18)
Hysterectomy only	0.87 (0.77-0.97)	0.87 (0.74-1.01)	0.89 (0.78-1.00)	0.83 (0.73-0.96)	1.01 (0.88-1.17)	0.97 (0.74-1.28)
Oophorectomy only	0.61 (0.30-1.21)	0.58 (0.21-1.59)	0.64 (0.30-1.33)	0.48 (0.19-1.19)	0.78 (0.33-1.83)	0.53 (0.07-3.93)
Oophorect. + hysterect.	0.86 (0.76-0.98)	0.87 (0.73-1.03)	0.94 (0.82-1.07)	0.86 (0.74-1.00)	0.92 (0.72-1.17)	1.05 (0.66-1.66)

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, hormone replacement therapy use, number of live births, smoking status, pack-years, and body mass index.

Supplementary table 5. Association of forced vital capacity (FVC) with age at natural menopause, by age group.

	40-55 years		56-59 years		60-62 years		63-65 years		66-70 years	
	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)
FVC (mL)										
Natural menopause at <45 years	1976	-48 (-74, -22)	1041	-52 (-82, -22)	1053	-36 (-65, -7)	1010	-23 (-53, 6)	1000	-41 (-71, -12)
Natural menopause at 45-47 years	2324	-25 (-48, -2)	1282	-23 (-51, 4)	1297	-5 (-32, 21)	1105	-1 (-29, 27)	1284	-12 (-39, 14)
Natural menopause at 48-53 years	9788	Ref.	8174	Ref.	7309	Ref.	5779	Ref.	5743	Ref.
Natural menopause at 54-55 years	703	10 (-27, 48)	2612	0 (-20, 20)	2351	-16 (-37, 4)	1831	7 (-16, 30)	1498	-10 (-35, 15)
Natural menopause at 56+ years	-	-	1147	-5 (-34, 23)	1710	-9 (-32, 15)	1393	21 (-5, 46)	1296	8 (-18, 35)
	p-trend = 4.5x10 ⁻⁶		p-trend = 0.004		p-trend = 0.3		p-trend = 0.006		p-trend = 5.7x10 ⁻⁴	
FVC (mL) – excluding HRT ever users										
Natural menopause at <45 years	992	-71 (-107, -35)	332	-70 (-121, -18)	361	-36 (-85, 12)	373	-27 (-74, 21)	508	-49 (-91, -7)
Natural menopause at 45-47 years	1656	-24 (-51, 3)	638	-36 (-74, 2)	558	-15 (-55, 25)	474	5 (-37, 48)	623	-2 (-41, 36)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Natural menopause at 54-55 years	573	35 (-8, 78)	1765	-2 (-27, 22)	1223	-30 (-58, -1)	845	22 (-12, 55)	696	30 (-7, 67)
Natural menopause at 56+ years	-	-	791	-5 (-39, 30)	877	-9 (-42, 24)	621	35 (-3, 73)	561	25 (-16, 65)
	p-trend = 8.2x10 ⁻⁷		p-trend = 0.03		p-trend = 1.0		p-trend = 0.03		p-trend = 8.4x10 ⁻⁵	
FVC (mL) – excluding HRT ever users and ever smokers										
Natural menopause at <45 years	613	-48 (-92, -3)	200	-79 (-144, -13)	224	2 (-59, 62)	214	-6 (-67, 56)	303	-11 (-64, 42)
Natural menopause at 45-47 years	1132	-22 (-55, 11)	422	-26 (-73, 20)	346	-17 (-67, 33)	311	24 (-27, 76)	412	-12 (-58, 35)
Natural menopause at 48-53 years	5537	Ref.	3710	Ref.	2770	Ref.	1891	Ref.	2059	Ref.
Natural menopause at 54-55 years	433	31 (-18, 80)	1326	-11 (-40, 18)	918	-36 (-70, -3)	613	32 (-7, 71)	512	17 (-25, 60)
Natural menopause at 56+ years	-	-	590	-2 (-42, 38)	653	-18 (-56, 20)	465	42 (-2, 86)	434	29 (-17, 74)
	p-trend = 0.004		p-trend = 0.2		p-trend = 0.2		p-trend = 0.2		p-trend = 0.02	
FVC (mL) – excluding HRT ever users, ever smokers, and extreme BMI										
Natural menopause at <45 years	454	-47 (-98, 5)	149	-81 (-157, -5)	160	14 (-57, 85)	147	12 (-61, 85)	210	-14 (-78, 51)
Natural menopause at 45-47 years	885	-25 (-63, 12)	326	-37 (-89, 16)	275	-17 (-72, 39)	236	-9 (-68, 50)	324	-9 (-62, 45)
Natural menopause at 48-53 years	4380	Ref.	2953	Ref.	2153	Ref.	1482	Ref.	1608	Ref.
Natural menopause at 54-55 years	341	33 (-23, 88)	1055	-3 (-35, 29)	705	-29 (-67, 8)	474	40 (-4, 85)	386	6 (-44, 56)
Natural menopause at 56+ years	-	-	446	19 (-27, 65)	473	-10 (-54, 34)	325	23 (-29, 75)	326	22 (-32, 75)
	p-trend = 0.007		p-trend = 0.07		p-trend = 0.4		p-trend = 0.4		p-trend = 0.1	

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, hormone replacement therapy use, number of live births, smoking status, pack-years, and body mass index. Reference group: Women with natural menopause at age 48-53. *P*-trend is from model with age at menopause as continuous variable.

Supplementary table 6. Association of forced expiratory volume in 1 second (FEV1) with age at natural menopause, by age group.

	40-55 years		56-59 years		60-62 years		63-65 years		66-70 years	
	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)
FEV1 (mL/s)										
Natural menopause at <45 years	1976	-41 (-63, -19)	1041	-44 (-69, -19)	1053	-36 (-60, -11)	1010	-24 (-49, 1)	1000	-30 (-55, -5)
Natural menopause at 45-47 years	2324	-26 (-45, -7)	1282	-11 (-34, 12)	1297	-3 (-25, 19)	1105	-13 (-37, 11)	1284	-15 (-38, 8)
Natural menopause at 48-53 years	9788	Ref.	8174	Ref.	7309	Ref.	5779	Ref.	5743	Ref.
Natural menopause at 54-55 years	703	-2 (-33, 30)	2612	6 (-11, 23)	2351	-13 (-31, 4)	1831	2 (-18, 21)	1498	-2 (-23, 20)
Natural menopause at 56+ years	-	-	1147	-4 (-29, 20)	1710	-3 (-23, 17)	1393	19 (-3, 40)	1296	6 (-17, 28)
	p-trend = 1.1x10 ⁻⁵		p-trend = 0.002		p-trend = 0.05		p-trend = 6.2x10 ⁻⁴		p-trend = 6.9x10 ⁻⁴	
FEV1 (mL/s) – <u>excluding HRT ever users</u>										
Natural menopause at <45 years	992	-54 (-84, -25)	332	-57 (-100, -14)	361	-38 (-78, 3)	373	-26 (-66, 14)	508	-49 (-85, -14)
Natural menopause at 45-47 years	1656	-24 (-47, -2)	638	-19 (-51, 12)	558	-17 (-51, 16)	474	-13 (-49, 23)	623	-10 (-43, 22)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Natural menopause at 54-55 years	573	17 (-18, 53)	1765	3 (-17, 24)	1223	-20 (-44, 4)	845	8 (-20, 37)	696	25 (-6, 56)
Natural menopause at 56+ years	-	-	791	-2 (-31, 27)	877	-3 (-30, 25)	621	36 (3, 68)	561	21 (-13, 55)
	p-trend = 6.6x10 ⁻⁶		p-trend = 0.01		p-trend = 0.3		p-trend = 0.005		p-trend = 1.5x10 ⁻⁵	
FEV1 (mL/s) – <u>excluding HRT ever users and ever smokers</u>										
Natural menopause at <45 years	613	-38 (-75, -1)	200	-73 (-128, -18)	224	-2 (-52, 48)	214	-9 (-60, 42)	303	-10 (-54, 35)
Natural menopause at 45-47 years	1132	-18 (-45, 9)	422	-1 (-39, 38)	346	-21 (-62, 20)	311	15 (-28, 59)	412	-7 (-46, 32)
Natural menopause at 48-53 years	5537	Ref.	3710	Ref.	2770	Ref.	1891	Ref.	2059	Ref.
Natural menopause at 54-55 years	433	11 (-30, 51)	1326	-7 (-32, 17)	918	-27 (-54, 1)	613	20 (-13, 53)	512	18 (-18, 54)
Natural menopause at 56+ years	-	-	590	-1 (-35, 32)	653	-12 (-43, 20)	465	39 (2, 76)	434	28 (-10, 67)
	p-trend = 0.008		p-trend = 0.2		p-trend = 0.6		p-trend = 0.1		p-trend = 0.02	
FEV1 (mL/s) – <u>excluding HRT ever users, ever smokers, and extreme BMI</u>										
Natural menopause at <45 years	454	-37 (-80, 6)	149	-72 (-134, -9)	160	8 (-51, 68)	147	0 (-61, 61)	210	-6 (-60, 48)
Natural menopause at 45-47 years	885	-20 (-51, 11)	326	-13 (-57, 30)	275	-19 (-65, 27)	236	-8 (-57, 41)	324	-4 (-49, 40)
Natural menopause at 48-53 years	4380	Ref.	2953	Ref.	2153	Ref.	1482	Ref.	1608	Ref.
Natural menopause at 54-55 years	341	11 (-35, 57)	1055	-1 (-28, 26)	705	-21 (-52, 11)	474	30 (-7, 67)	386	7 (-35, 48)
Natural menopause at 56+ years	-	-	446	10 (-28, 48)	473	-4 (-41, 33)	325	18 (-25, 62)	326	23 (-21, 68)
	p-trend = 0.02		p-trend = 0.1		p-trend = 0.8		p-trend = 0.3		p-trend = 0.1	

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, hormone replacement therapy use, number of live births, smoking status, pack-years, and body mass index. Reference group: Women with natural menopause at age 48-53. *P*-trend is from model with age at menopause as continuous variable.

Supplementary table 7. Association of spirometric restriction (FVC<LLN) with age at natural menopause, by age group.

	40-55 years		56-59 years		60-62 years		63-65 years		66-70 years	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
FVC < LLN										
Natural menopause at <45 years	1976	1.05 (0.90-1.23)	1041	1.40 (1.18-1.66)	1053	1.21 (1.02-1.44)	1010	1.15 (0.95-1.38)	1000	1.19 (0.99-1.43)
Natural menopause at 45-47 years	2324	1.12 (0.98-1.28)	1282	1.06 (0.89-1.25)	1297	1.02 (0.86-1.20)	1105	1.06 (0.88-1.27)	1284	1.08 (0.91-1.28)
Natural menopause at 48-53 years	9788	Ref.	8174	Ref.	7309	Ref.	5779	Ref.	5743	Ref.
Natural menopause at 54-55 years	703	0.92 (0.73-1.17)	2612	0.92 (0.81-1.05)	2351	1.12 (0.98-1.27)	1831	0.99 (0.84-1.15)	1498	1.05 (0.90-1.24)
Natural menopause at 56+ years	-	-	1147	1.03 (0.86-1.24)	1710	1.13 (0.97-1.31)	1393	0.95 (0.80-1.13)	1296	0.95 (0.79-1.13)
	p-trend = 0.1		p-trend = 5.4x10 ⁻⁴		p-trend = 0.8		p-trend = 0.05		p-trend = 0.02	
FVC < LLN – excluding HRT ever users										
Natural menopause at <45 years	992	1.07 (0.87-1.32)	332	1.48 (1.11-1.98)	361	1.34 (1.00-1.80)	373	1.06 (0.79-1.44)	508	1.30 (1.02-1.67)
Natural menopause at 45-47 years	1656	1.09 (0.93-1.28)	638	1.03 (0.81-1.30)	558	1.34 (1.04-1.71)	474	0.92 (0.69-1.23)	623	1.12 (0.88-1.42)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Natural menopause at 54-55 years	573	0.80 (0.61-1.05)	1765	0.94 (0.80-1.11)	1223	1.26 (1.05-1.52)	845	0.91 (0.72-1.14)	696	0.89 (0.70-1.13)
Natural menopause at 56+ years	-	-	791	1.03 (0.83-1.28)	877	1.09 (0.88-1.36)	621	0.84 (0.64-1.10)	561	0.78 (0.60-1.03)
	p-trend = 0.05		p-trend = 0.08		p-trend = 0.5		p-trend = 0.3		p-trend = 5.8x10 ⁻⁴	
FVC < LLN – excluding HRT ever users and ever smokers										
Natural menopause at <45 years	613	0.86 (0.65-1.13)	200	1.65 (1.14-2.38)	224	1.18 (0.80-1.74)	214	0.91 (0.58-1.41)	303	1.07 (0.75-1.52)
Natural menopause at 45-47 years	1132	1.03 (0.84-1.25)	422	0.98 (0.72-1.31)	346	1.07 (0.76-1.50)	311	0.81 (0.55-1.19)	412	1.17 (0.87-1.59)
Natural menopause at 48-53 years	5537	Ref.	3710	Ref.	2770	Ref.	1891	Ref.	2059	Ref.
Natural menopause at 54-55 years	433	0.80 (0.58-1.09)	1326	1.02 (0.85-1.23)	918	1.28 (1.02-1.59)	613	0.90 (0.68-1.20)	512	0.90 (0.67-1.21)
Natural menopause at 56+ years	-	-	590	1.03 (0.80-1.33)	653	1.07 (0.83-1.39)	465	0.74 (0.53-1.03)	434	0.71 (0.51-1.00)
	p-trend = 0.7		p-trend = 0.4		p-trend = 0.5		p-trend = 0.6		p-trend = 0.01	
FVC < LLN – excluding HRT ever users, ever smokers, and extreme BMI										
Natural menopause at <45 years	454	0.97 (0.70-1.35)	149	1.62 (1.03-2.53)	160	1.26 (0.77-2.04)	147	0.70 (0.38-1.29)	210	1.13 (0.73-1.76)
Natural menopause at 45-47 years	885	1.01 (0.80-1.29)	326	1.10 (0.78-1.55)	275	1.06 (0.70-1.59)	236	0.96 (0.61-1.52)	324	1.18 (0.83-1.68)
Natural menopause at 48-53 years	4380	Ref.	2953	Ref.	2153	Ref.	1482	Ref.	1608	Ref.
Natural menopause at 54-55 years	341	0.72 (0.50-1.06)	1055	0.94 (0.75-1.18)	705	1.34 (1.02-1.74)	474	0.84 (0.59-1.19)	386	1.01 (0.71-1.43)
Natural menopause at 56+ years	-	-	446	0.90 (0.66-1.24)	473	1.17 (0.86-1.61)	325	0.78 (0.51-1.18)	326	0.71 (0.48-1.07)
	p-trend = 0.4		p-trend = 0.08		p-trend = 0.3		p-trend = 0.9		p-trend = 0.04	

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, hormone replacement therapy use, number of live births, smoking status, pack-years, and body mass index. Reference group: Women with natural menopause at age 48-53. *P*-trend is from model with age at menopause as continuous variable.

Supplementary table 8. Association of airflow obstruction (FEV1/FVC<LLN) with age at natural menopause, by age group.

	40-55 years		56-59 years		60-62 years		63-65 years		66-70 years	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
FEV1/FVC < LLN										
Natural menopause at <45 years	1976	1.21 (1.00-1.47)	1041	1.25 (1.01-1.55)	1053	1.19 (0.96-1.48)	1010	1.14 (0.91-1.44)	1000	1.00 (0.80-1.26)
Natural menopause at 45-47 years	2324	1.12 (0.95-1.33)	1282	0.89 (0.71-1.10)	1297	1.05 (0.86-1.30)	1105	1.23 (0.99-1.52)	1284	0.99 (0.81-1.22)
Natural menopause at 48-53 years	9788	Ref.	8184	Ref.	7309	Ref.	5779	Ref.	5743	Ref.
Natural menopause at 54-55 years	703	1.04 (0.76-1.43)	2612	0.85 (0.71-1.01)	2351	1.05 (0.88-1.25)	1831	1.08 (0.89-1.32)	1498	0.94 (0.76-1.15)
Natural menopause at 56+ years	-	-	1147	1.02 (0.80-1.29)	1710	0.88 (0.71-1.09)	1393	0.99 (0.79-1.24)	1296	1.01 (0.8q-1.26)
	p-trend = 0.1		p-trend = 0.03		p-trend = 0.1		p-trend = 0.1		p-trend = 0.8	
FEV1/FVC < LLN – <u>excluding HRT ever users</u>										
Natural menopause at <45 years	922	1.10 (0.84-1.44)	332	1.25 (0.86-1.81)	361	1.43 (1.00-2.05)	373	1.17 (0.79-1.71)	508	1.26 (0.92-1.71)
Natural menopause at 45-47 years	1656	1.16 (0.94-1.42)	638	0.85 (0.61-1.17)	558	1.09 (0.79-1.51)	474	1.39 (0.99-1.96)	623	1.12 (0.84-1.50)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Natural menopause at 54-55 years	573	1.00 (0.70-1.43)	1765	0.80 (0.64-1.01)	1223	1.09 (0.85-1.41)	845	1.13 (0.84-1.53)	696	0.93 (0.69-1.27)
Natural menopause at 56+ years	-	-	791	0.96 (0.71-1.31)	877	0.75 (0.54-1.05)	621	0.80 (0.54-1.18)	561	0.97 (0.69-1.35)
	p-trend = 0.5		p-trend = 0.09		p-trend = 0.07		p-trend = 0.03		p-trend = 0.08	
FEV1/FVC < LLN – <u>excluding HRT ever users and ever smokers</u>										
Natural menopause at <45 years	613	1.09 (0.74-1.61)	200	1.48 (0.88-2.49)	224	1.10 (0.61-1.99)	214	0.98 (0.50-1.92)	303	0.92 (0.55-1.51)
Natural menopause at 45-47 years	1132	1.14 (0.86-1.50)	422	0.59 (0.34-1.00)	346	1.28 (0.80-2.03)	311	1.12 (0.67-1.90)	412	1.03 (0.69-1.54)
Natural menopause at 48-53 years	5537	Ref.	3710	Ref.	2770	Ref.	1891	Ref.	2059	Ref.
Natural menopause at 54-55 years	433	1.05 (0.68-1.64)	1326	0.89 (0.68-1.18)	918	1.05 (0.75-1.47)	613	1.10 (0.74-1.64)	512	0.87 (0.59-1.29)
Natural menopause at 56+ years	-	-	590	1.06 (0.74-1.53)	653	0.82 (0.54-1.25)	465	0.87 (0.54-1.42)	434	0.90 (0.59-1.37)
	p-trend = 0.8		p-trend = 0.4		p-trend = 0.4		p-trend = 0.8		p-trend = 0.6	
FEV1/FVC < LLN – <u>excluding HRT ever users, ever smokers, and extreme BMI</u>										
Natural menopause at <45 years	454	1.12 (0.73-1.70)	149	1.50 (0.83-2.72)	160	0.88 (0.43-1.77)	147	1.29 (0.65-2.58)	210	0.79 (0.43-1.43)
Natural menopause at 45-47 years	885	1.04 (0.77-1.42)	326	0.65 (0.37-1.16)	275	1.30 (0.80-2.12)	236	1.24 (0.71-2.18)	324	0.99 (0.64-1.53)
Natural menopause at 48-53 years	4380	Ref.	2953	Ref.	2153	Ref.	1482	Ref.	1608	Ref.
Natural menopause at 54-55 years	341	1.08 (0.68-1.73)	1055	0.82 (0.60-1.13)	705	1.05 (0.73-1.51)	474	1.08 (0.69-1.67)	386	0.90 (0.59-1.37)
Natural menopause at 56+ years	-	-	446	1.17 (0.79-1.73)	473	0.86 (0.55-1.34)	325	0.94 (0.55-1.60)	326	0.80 (0.49-1.29)
	p-trend = 0.8		p-trend = 0.6		p-trend = 0.7		p-trend = 0.5		p-trend = 0.6	

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, hormone replacement therapy use, number of live births, smoking status, pack-years, and body mass index. Reference group: Women with natural menopause at age 48-53. *P*-trend is from model with age at menopause as continuous variable.

Supplementary table 9. Association of lung function with age at hysterectomy, by age group, among women who have never taken HRT.

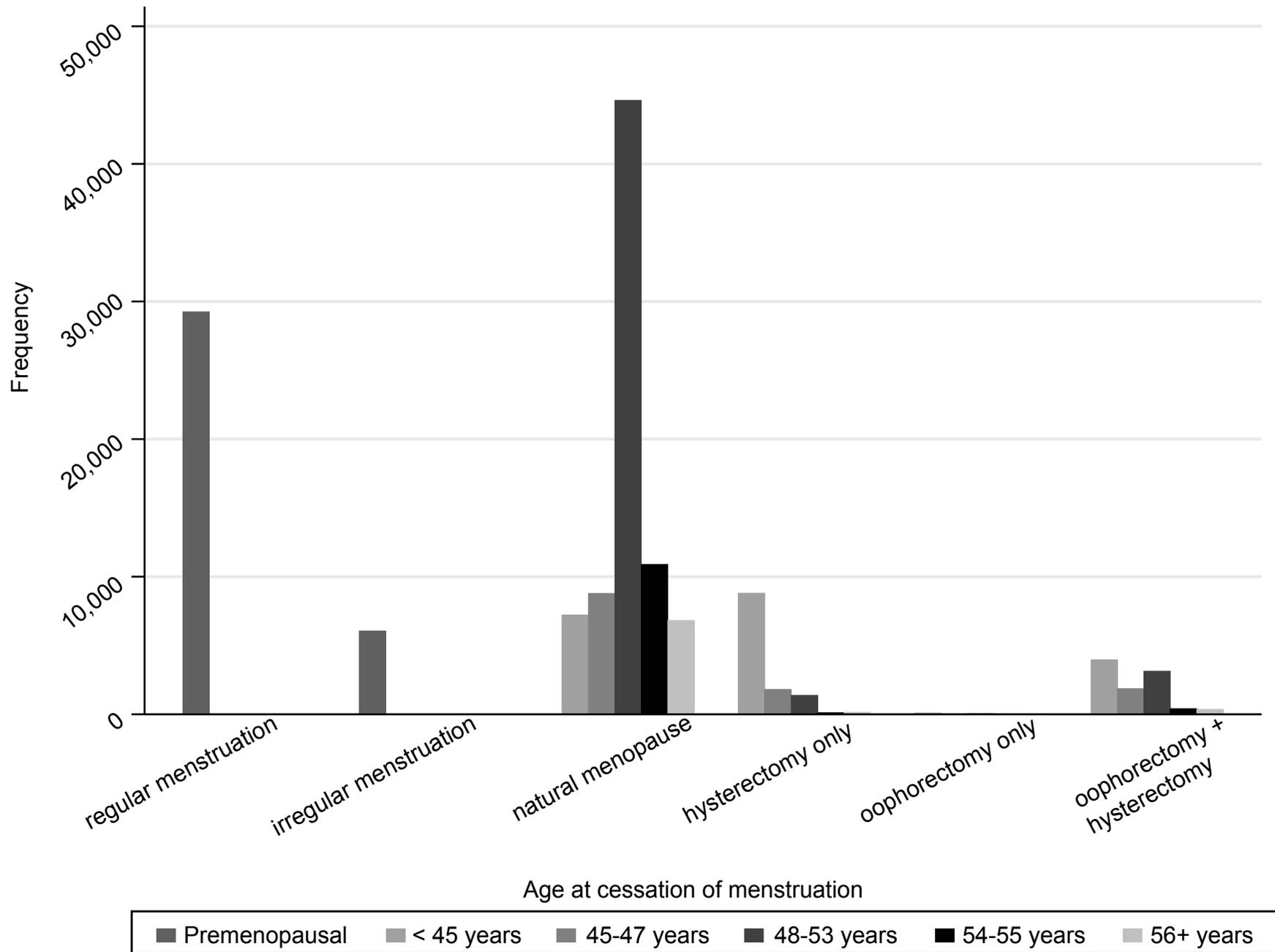
	40-55 years		56-59 years		60-62 years		63-65 years		66-70 years	
	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)	N	Difference (95% CI)
FVC (mL)										
Hysterectomy at < 45 years	1424	8 (-25, 41)	421	-32 (-78, 14)	339	-44 (-94, 6)	303	-47 (-99, 5)	331	-19 (-70, 32)
Hysterectomy at 45-47 years	271	-46 (-104, 12)	119	-109 (-193, -25)	79	-26 (-126, 73)	82	-66 (-162, 30)	95	19 (-72, 111)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Hysterectomy at 48-53 years	173	-19 (-89, 52)	87	-8 (-106, 90)	90	-51 (-144, 43)	65	-11 (-118, 96)	75	12 (-90, 115)
Hysterectomy at 54-55 years	7	45 (-300, 391)	15	-9 (-243, 235)	9	83 (-210, 375)	5	91 (-290, 473)	6	99 (-258, 456)
Hysterectomy at 56+ years	-	-	7	-40 (-382, 303)	6	-276 (-634, 83)	11	-102 (-360, 156)	15	43 (-183, 269)
	p-trend = 1.0		p-trend = 0.5		p-trend = 1.0		p-trend = 0.2		p-trend = 0.2	
FEV1 (mL/s)										
Hysterectomy at < 45 years	1424	9 (-18, 37)	421	-33 (-71, 6)	339	-31 (-73, 10)	303	-39 (-83, 5)	331	-7 (-50, 36)
Hysterectomy at 45-47 years	271	-31 (-79, 18)	119	-81 (-151, -10)	79	2 (-82, 85)	82	-59 (-140, 23)	95	42 (-35, 119)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Hysterectomy at 48-53 years	173	-27 (-86, 33)	87	-10 (-92, 72)	90	-31 (-109, 48)	65	-8 (-99, 83)	75	40 (-47, 126)
Hysterectomy at 54-55 years	7	93 (-198, 383)	15	-7 (-202, 189)	9	64 (-181, 309)	5	80 (-245, 405)	6	85 (-216, 385)
Hysterectomy at 56+ years	-	-	7	-13 (-300, 274)	6	-153 (-453, 148)	11	-55 (-274, 165)	15	85 (-105, 276)
	p-trend = 0.7		p-trend = 0.5		p-trend = 0.8		p-trend = 0.2		p-trend = 0.1	
	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)	N	OR (95% CI)
FVC<LLN										
Hysterectomy at < 45 years	1424	0.90 (0.74-1.10)	421	1.04 (0.78-1.37)	339	1.54 (1.15-2.07)	303	1.21 (0.87-1.67)	331	1.12 (0.82-1.52)
Hysterectomy at 45-47 years	271	1.20 (0.86-1.67)	119	1.01 (0.61-1.67)	79	0.72 (0.35-1.48)	82	1.38 (0.77-2.47)	95	0.80 (0.43-1.50)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Hysterectomy at 48-53 years	173	1.16 (0.76-1.75)	87	0.63 (0.33-1.23)	90	0.82 (0.42-1.60)	65	1.26 (0.62-2.53)	75	0.84 (0.42-1.65)
Hysterectomy at 54-55 years	7	0.95 (0.11-8.06)	15	0.94 (0.24-3.63)	9	0.96 (0.14-6.41)	5	1.00 (1.00-1.00)	6	1.40 (0.15-12.65)
Hysterectomy at 56+ years	-	-	7	0.91 (0.11-7.88)	6	3.18 (0.54-18.70)	11	2.28 (0.58-8.96)	15	1.00 (1.00-1.00)
	p-trend = 0.3		p-trend = 0.7		p-trend = 0.07		p-trend = 0.2		p-trend = 0.9	
FEV1/FVC<LLN										
Hysterectomy at < 45 years	1424	0.98 (0.76-1.28)	421	1.34 (0.94-1.90)	339	1.01 (0.65-1.57)	303	1.09 (0.67-1.77)	331	0.93 (0.61-1.43)
Hysterectomy at 45-47 years	271	0.88 (0.53-1.45)	119	0.97 (0.47-2.00)	79	1.64 (0.76-3.57)	82	0.83 (0.32-2.17)	95	0.38 (0.13-1.10)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Hysterectomy at 48-53 years	173	1.47 (0.88-2.44)	87	1.66 (0.81-3.38)	90	0.87 (0.36-2.12)	65	0.92 (0.31-2.66)	75	0.63 (0.24-1.67)
Hysterectomy at 54-55 years	7	1.00 (1.00-1.00)	15	1.00 (1.00-1.00)	9	3.11 (0.37-26.11)	5	1.00 (1.00-1.00)	6	2.08 (0.22-19.86)
Hysterectomy at 56+ years	-	-	7	1.00 (1.00-1.00)	6	1.00 (1.00-1.00)	11	1.00 (1.00-1.00)	15	0.71 (0.09-5.64)
	p-trend = 0.1		p-trend = 0.6		p-trend = 0.7		p-trend = 0.2		p-trend = 0.2	

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, HRT use, number of live births, smoking status, pack-years, and body mass index. Ref. group: Women with natural menopause at age 48-53. P-trend is from model with age at hysterectomy as continuous variable.

Supplementary table 10. Association of lung function with age at oophorectomy + hysterectomy, by age group, among women who have never taken HRT.

	40-55 years		56-59 years		60-62 years		63-65 years		66-70 years	
	N	Difference/OR (95% CI)								
FVC (mL)										
Oophor.+hysterect. at < 45 years	82	-55 (-168, 58)	15	71 (-165, 307)	20	-54 (-250, 141)	36	-74 (-218, 70)	41	-179 (-317, -40)
Oophor.+hysterect. at 45-47 years	65	70 (-46, 185)	13	-91 (-345, 162)	9	-167 (-459, 124)	8	-87 (-391, 217)	18	-57 (-264, 150)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Oophor.+hysterect. at 48-53 years	247	-55 (-116, 7)	121	20 (-64, 104)	94	87 (-5, 178)	80	-77 (-175, 21)	151	-2 (-75, 72)
Oophor.+hysterect. at 54-55 years	2	-622 (-1267, 24)	7	-391 (-736, -47)	7	115 (-215, 445)	5	-54 (-439, 330)	7	272 (-59, 603)
Oophor.+hysterect. at 56+ years	-	-	14	140 (-104, 383)	22	-1 (-188, 188)	15	-160 (-383, 63)	32	-69 (-225, 87)
		p-trend = 0.5		p-trend = 0.5		p-trend = 0.9		p-trend = 1.0		p-trend = 0.2
FEV1 (mL/s)										
Oophor.+hysterect. at < 45 years	82	-16 (-111, 79)	15	17 (-181, 215)	20	-28 (-191, 136)	36	-62 (-185, 60)	41	-114 (-231, 3)
Oophor.+hysterect. at 45-47 years	65	91 (-6, 189)	13	-70 (-282, 142)	9	-101 (-345, 143)	8	-78 (-336, 179)	18	0 (-175, 174)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Oophor.+hysterect. at 48-53 years	247	-33 (-85, 19)	121	21 (-49, 92)	94	76 (-1, 152)	80	-60 (-143, 22)	151	24 (-38, 86)
Oophor.+hysterect. at 54-55 years	2	-463 (-1007, 81)	7	-271 (-559, 17)	7	79 (-197, 355)	5	-100 (-426, 225)	7	229 (-51, 508)
Oophor.+hysterect. at 56+ years	-	-	14	159 (-45, 363)	22	36 (-120, 192)	15	-109 (-298, 80)	32	-40 (-171, 92)
		p-trend = 0.3		p-trend = 0.7		p-trend = 0.7		p-trend = 0.7		p-trend = 0.5
	N	OR (95% CI)								
FVC<LLN										
Oophor.+hysterect. at < 45 years	82	1.91 (1.05-3.49)	15	0.36 (0.05-2.84)	20	1.30 (0.40-4.15)	36	1.89 (0.87-4.09)	41	2.03 (0.98-4.21)
Oophor.+hysterect. at 45-47 years	65	0.59 (0.26-1.33)	13	1.41 (0.30-6.70)	9	3.01 (0.64-14.25)	8	1.19 (0.19-7.29)	18	1.28 (0.39-4.15)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Oophor.+hysterect. at 48-53 years	247	1.22 (0.87-1.72)	121	0.81 (0.47-1.37)	94	0.51 (0.25-1.03)	80	1.29 (0.70-2.37)	151	0.85 (0.53-1.36)
Oophor.+hysterect. at 54-55 years	2	9.57 (0.57-161.05)	7	8.24 (1.69-40.13)	7	1.17 (0.13-10.51)	5	2.70 (0.33-21.79)	7	0.53 (0.04-6.49)
Oophor.+hysterect. at 56+ years	-	-	14	0.86 (0.18-4.04)	22	1.64 (0.54-5.02)	15	1.47 (0.41-5.20)	32	0.71 (0.24-2.08)
		p-trend = 0.2		p-trend = 0.9		p-trend = 0.8		p-trend = 0.1		p-trend = 0.1
FEV1/FVC<LLN										
Oophor.+hysterect. at < 45 years	82	1.92 (1.05-3.49)	15	0.36 (0.05-2.84)	20	1.30 (0.40-4.15)	36	1.89 (0.87-4.09)	41	2.03 (0.98-4.21)
Oophor.+hysterect. at 45-47 years	65	0.59 (0.26-1.33)	13	1.41 (0.30-6.70)	9	3.01 (0.64-14.25)	8	1.19 (0.19-7.29)	18	1.28 (0.39-4.15)
Natural menopause at 48-53 years	7773	Ref.	5189	Ref.	3881	Ref.	2745	Ref.	2859	Ref.
Oophor.+hysterect. at 48-53 years	247	1.22 (0.87-1.72)	121	0.81 (0.47-1.37)	94	0.51 (0.25-1.03)	80	1.29 (0.70-2.37)	151	0.85 (0.53-1.36)
Oophor.+hysterect. at 54-55 years	2	9.57 (0.57-161.05)	7	8.24 (1.69-40.13)	7	1.17 (0.13-10.51)	5	2.70 (0.33-21.79)	7	0.53 (0.04-6.49)
Oophor.+hysterect. at 56+ years	-	-	14	0.86 (0.18-4.04)	22	1.64 (0.54-5.02)	15	1.47 (0.41-5.20)	32	0.71 (0.24-2.08)
		p-trend = 0.2		p-trend = 0.8		p-trend = 0.8		p-trend = 0.1		p-trend = 0.1

Model 3: Adjusted for centre, age, ethnicity, standing height, Townsend deprivation index, age at menarche, oral contraceptive use, HRT use, number of live births, smoking status, pack-years, and body mass index. Ref. group: Women with natural menopause at age 48-53. P-trend is from model with age at hysterectomy as continuous variable.



Supplementary figure 1. Age at cessation of menstruation by menstrual status.