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Early View

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Age at menopause and lung function: a Mendelian Randomization study

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Age at menopause and lung function: a Mendelian Randomization study

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Take home message

Using Mendelian randomization, an approach not affected by classical confounding, we show a protective effect of early menopause on airflow obstruction. This points to the importance of investigating the effects of female sex hormones on the airways.

Abstract

In observational studies, early menopause is associated with lower FVC and a higher risk of spirometric restriction, but not airflow obstruction. It is however unclear if this association is causal. We therefore used a Mendelian randomization (MR) approach, which is not affected by classical confounding, to assess the effect of age at natural menopause on lung function.

We included 94,742 naturally post-menopausal women from UK Biobank and performed MR analyses on the effect of age at menopause on FEV_1, FVC, FEV_1/FVC, spirometric restriction (FVC<LLN) and airflow obstruction (FEV_1/FVC<LLN). We used the inverse variance-weighted (IVW) method, as well as methods that adjust for pleiotropy, and compared MR with observational analyses.

The MR analyses showed higher FEV_1/FVC and a 15% lower risk of airflow obstruction for women with early (<45 years) compared to normal (45-55) menopause. Despite some evidence of pleiotropy, the results were consistent when using MR methods robust to pleiotropy. Similar results were found among never- and ever-smokers, while the protective effect seemed less strong in women ever using menopause hormone treatment and in overweight women. There was no strong evidence of association with FVC or spirometric restriction. In observational analyses of the same dataset, early menopause was associated with a pronounced reduction in FVC and a 13% higher spirometric restriction risk.

Our MR results suggest that early menopause has a protective effect on airflow obstruction. Further studies are warranted to better understand the inconsistency with observational findings, and to investigate the underlying mechanisms and role of female sex hormones.

Keywords: Early menopause; Airflow obstruction; Mendelian randomization; Sex hormones

Introduction

Women are more susceptible to develop chronic obstructive pulmonary disease (COPD) than men, especially among never-smokers,[1] and it is speculated that these sex differences may arise partly from distinct sex hormone patterns during life.[2] A major shift in sex hormone levels occurs during menopause. Age at natural menopause shows considerable variability between women, normally occurring between 45 to 55 years of age, with an average of 51 years in European women.[3] As populations age, the proportion of the female population living in a post-menopausal state is increasing and we need to better understand the impact of this major biological event on respiratory health and health in general.

A recent systematic review supports an association of menopause with lower forced expiratory volume in one second (FEV_1) and lower forced vital capacity (FVC).[4] A large study in the UK Biobank showed that women with an earlier age at menopause had lower FEV_1 and FVC, and a higher risk of spirometric restriction while no association was found for airflow obstruction.[5] These observational studies may suffer from residual confounding even when the analyses are adjusted for known confounders, including anthropometric, lifestyle, social-economic, and reproductive characteristics. Potential confounders may also include early life events, diet and physical activity, and there could be other, yet unrecognized, factors associated with both age at menopause and lung function.[6, 7]

The Mendelian Randomization (MR) approach can help to assess the causal effect of age at menopause on lung function.[8] With MR, genetic variants (single nucleotide polymorphisms, SNPs) are used as proxies ("instrumental variables") for age at menopause.[9] The alleles of a genetic variant are randomly allocated at conception and therefore not affected by classical confounding. Finding that the SNPs predisposing to earlier age at menopause are associated with lung function would provide indirect evidence of a causal effect, as long as the assumptions underlying MR hold (Figure 1).[8] Of particular concern is pleiotropy, which is present when a SNP is also associated with other traits affecting lung function, independently from age at menopause.[8, 10]

In the current study, we used MR to estimate the effect of age at menopause on five lung function outcomes (FVC, FEV_1/FVC, FEV_1, spirometric restriction and airflow obstruction) using data from the UK Biobank. We categorized menopause as early, normal and late menopause to allow the investigation of possible non-linear effects. Moreover, early menopause is of particular clinical interest and has been most commonly investigated for association with health outcomes in previous studies. We assessed the robustness of our main MR results using methods to investigate and adjust for pleiotropy, and we performed subgroup analyses to investigate whether the effect of age at menopause on lung function varied according to smoking status, use of menopause hormone therapy (MHT) and body mass index (BMI). We also performed classical observational analyses on the same dataset, for comparison with MR.

Methods

Detailed methods are provided in the online data supplement.

Study population

We included naturally post-menopausal white women from the very large, population-based UK Biobank (UKB) study [11], and excluded women with surgical menopause and women with extreme age at menopause (<40 or >60). Age at natural menopause was based on self-reported age at which 'periods stopped', and was categorized as early (40-45 years), normal (45-55), or late (55-60), using normal as the reference category. We investigated the continuous outcomes FEV_1, FVC and FEV_1/FVC (best measure), as well as the binary outcomes spirometric restriction defined as FVC< lower limit of normal (LLN), and airflow obstruction defined as FEV_1/FVC<LLN. The LLN was based on the Global Lung Function Initiative 2012.[12]

SNP selection

Based on published genome-wide association studies (GWAS), we identified 80 SNPs associated with continuous age at menopause at a p-value threshold of $5x10^{-8}$.[13–18] After removing SNPs with F-statistic ≤10 to avoid weak instrument bias and SNPs highly correlated with each other (r^2≥0.8), 63 SNPs remained that jointly explained 6% of the UKB population variance of age at menopause.[19] Of the selected SNPs, 39 SNPs were strong instruments for early menopause and 40 for late menopause.

MR analyses

As our main analysis, we estimated the causal effect of early and late menopause on lung function, but we also performed MR analyses considering age at menopause as a continuous variable as secondary analyses. For each of the included SNPs we obtained two estimates from UKB (Figure 1); one for the association of the SNP with early and late menopause versus normal menopause (GX), using logistic regression adjusted for centre, first 10 ancestry principal components and three genotyping batches; and one for the association with the lung function outcomes (GY), using logistic (airway obstruction and spirometric restriction) or linear (FEV_1/FVC, FVC, and FEV_1) regression adjusted for age, age^2, height, centre, 10 principal components and three batches. For each SNP, an MR estimate was derived as the ratio of GY over GX (Wald estimator) and its standard error obtained using the Delta method.[20] SNP-specific MR estimates were then pooled using an inverse-variance weighted (IVW) fixed-effect meta-analysis method that accounts for correlation between SNPs (R package *MendelianRandomization*).[19, 21] We used the IVW two-sample MR method because the standard MR approach in a one-sample setting (as in our study), which is the two-stage least square (2SLS) method, does not account for pleiotropy.

<u>Assessing pleiotropy</u>

The presence of pleiotropy was investigated using between-instrument heterogeneity of the IVW MR estimates, based on I^2 statistic and Q test.[22] In secondary analyses we investigated the robustness of our findings to pleiotropy using MR methods based on different assumptions about the direction of possible pleiotropic effects: 1) IVW random-effect meta-analysis (IVW-R, assumes random pleiotropic effects); 2) weighted median analysis (assumes that at least 50% of the SNPs are valid IVs with no assumption on the direction of pleiotropic effects); 3) MR-Egger regression with penalized weights (assumes directional pleiotropic effects); and 4) MR-PRESSO (corrects for horizontal pleiotropy by removing pleiotropic outlier SNPs).[10, 23–25] Furthermore, we *a priori* considered height, BMI, and age at menarche as potential sources of pleiotropy. We excluded SNPs that were associated with these traits at a p-value $<7.9 \times 10^{-4}$ (Bonferroni correction, 0.05/63) based on information from the online PhenoScanner.[26]

<u>Sensitivity analyses</u>

We performed several sensitivity analyses to assess the robustness of our findings to choices made *a priori* for our MR analyses. These relate to the used MR method, the used sample, and the choice of SNPs used as instruments: 1) We performed the standard MR analysis for the one-sample setting, the 2SLS regression analysis, which assumes no pleiotropy similarly to the IVW fixed-effect method [27]; 2) We restricted the main MR analysis to exactly the same number of women included in the observational analysis to allow comparison between the two approaches (n=84,844); 3) We excluded asthmatic women as these women may have reversible airflow obstruction; and 4) We limited the MR analyses to the 54 SNPs identified by the most recent and largest GWAS on age at menopause (Day *et al*. [18]) and did not adjust for correlation (the 54 SNPs are independent) or remove weak SNPs in these analyses. Finally, we used GX estimates for continuous age at menopause from Day et al. [18]) together with the GY estimates from UKB, to further investigate the robustness of our findings when using two independent data sources (two-sample MR) instead of a single dataset (one-sample MR).

<u>Subgroup analyses</u>

For the lung function outcomes with consistently significant findings, we performed subgroup analyses by smoking status (never/ever) as some evidence suggests that a longer exposure to female sex hormones might increase airway susceptibility to the effects of smoking.[28, 29] In addition, we investigated potential effect modification by MHT use (never/ever) and BMI (low vs. high based on a cut-off of 26kg/m² (median), since women taking hormonal therapy and obese women may still have high levels of female sex hormones after menopause.

Observational analyses

Earlier observational analyses in UKB examined age at menopause as a categorical variable divided into five groups.[5] For comparison with our MR findings, we performed observational analyses in UKB using three menopause categories. Moreover, in addition to confounders previously considered (centre, age, age^2, height, BMI, smoking groups, Townsend deprivation index, MHT use, number of live births, ever use of oral contraceptives, and age at menarche), we also included physical activity and education level.[6, 7, 30]

All analyses were performed using R.

Results

Population characteristics

From UKB, 94,742 white women having undergone natural menopausal were included in the MR analyses, of which 7,206 had early and 8,468 had late menopause (Table 1 and Supplementary Table S1). The mean age was 60 years and mean age at menopause 51 years; 57% of women never used MHT, 7% had spirometric restriction (FVC<LLN) and 8% had airflow obstruction (FEV_1/FVC<LLN). Women with late menopause were less likely to have ever smoked and to have ever used MHT compared to women with early menopause. Only 84,844 of these women had complete data on all confounders and were included in the observational analyses, and their characteristics were the same as the MR sample (Table 1 and Table S1).

Detailed results of all MR and observational analyses, separately for early and late menopause, can be found in Supplementary Table S2 (GX and GY effect estimates) and Table S3 (MR results).

MR analyses

For early menopause (Table 2), the MR analyses showed higher FEV_1 (5.55mL [0.92 to 10.18]), higher FEV_1/FVC (0.29% [0.22 to 0.36]), and 15% lower risk of airflow obstruction (OR 0.85 [0.82 to 0.89]), as compared to normal menopause (Figure 2 and Table S3). No effect of early menopause was found for FVC (-4.98mL [-10.5 to 0.53]) or spirometric restriction (OR 1.03 [0.99 to 1.08]).

For late menopause (Table 3), the MR analyses showed lower FEV_1 (-11.0mL [-16.4 to -5.68]) and lower FEV_1/FVC (-0.18% [-0.26 to -0.10]), and moderate higher risk of airflow obstruction (OR 1.06 [1.01 to 1.11]) (Figure 2 and Table S3). Late menopause was also borderline significantly associated with lower FVC (-7.10mL [-13.5 to -0.75]), but not with spirometric restriction (1.00 [0.95 to 1.05]).

There results were consistent when considering age at menopause as a continuous variable, with an increase in age at menopause associated with lower FEV_1, lower FEV_1/FVC, and a higher risk of obstruction (Supplementary Table S4).

<u>Assessing pleiotropy</u>

Heterogeneity was low for the analyses on spirometric restriction and airflow obstruction (I^2: 0 to 20%; Q p-value: 0.098 to $3.2x10^{-4}$; global test p-value: 0.05 to 0.22). For the continuous lung function outcomes, the high I^2 (46 to 53%), the significant Q test (p-value: $1.0x10^{-5}$ to $5.2x10^{-10}$) and significant global test of MR-PRESSO (p-value: <0.0005) suggested the presence of (horizontal) pleiotropy (Table S3). Correcting for horizontal pleiotropy by MR-PRESSO increased the effect estimate sizes but these were not significantly different from the original MR estimates (distortion test; p-value: 0.43 to 0.94).

Overall, the results from the other MR methods robust to pleiotropy were consistent with those from the main analysis (Figure 2 and Table S3). For FEV_1/FVC and airflow obstruction, a protective effect of early menopause was found for all MR methods, and for FVC and spirometric restriction, the MR estimates remained not significant, except for the MR-Egger estimate of early menopause on spirometric restriction (OR 1.12 [1.00 to 1.24]).

We further assessed the impact of pleiotropy by removing SNPs with potential pleiotropic effects. Out of 63 SNPs, 16 SNPs were previously associated with height, five with (adult) BMI and four with age at menarche. Removing these SNPs gave similar results for both FEV_1/FVC and airflow obstruction compared to the main analyses, indicating robustness to pleiotropy (Tables 2, 3 and S3). Yet, we found a small detrimental effect of early menopause on FVC when excluding possible pleiotropic SNPs (-6.77mL [-12.8 to -0.067]), but still no effect on spirometric restriction (OR 1.03 [0.98 to 1.08]).

Sensitivity analyses

Results consistent with the main analyses were found in all sensitivity analyses assessing the robustness of our findings to choices made *a priori* (Tables 2 and 3 for FEV_1/FVC and airflow obstruction; Table S3 for all outcomes). These related to the MR method used (one-sample 2SLS (Figure 2)), the sample used (same number as observational analyses and limited to non-asthmatics), and the choice of SNPs used as instruments (limiting to SNPs identified by Day et al. [18]). We also found consistent results when using GX estimates for continuous age at menopause from the literature (Day et al. [18]) and GY estimates from UKB (Table S4).

Subgroup analyses

We hypothesized a possible stronger effect in smokers, but found no statistically significant difference in MR estimates for FEV_1/FVC and airflow obstruction between ever- and never-smokers (Figure 3 and Table S5). In addition, we hypothesized that the protective effect of early menopause might be less evident in women who still have high levels of female sex hormones after menopause (i.e. MHT users and overweight/obese women), and our findings support these hypotheses (Figure 3 and Table S5). We found a significant difference in effect between never- and ever MHT users; the interaction was significant for airflow obstruction for both early and late menopause (p=0.002 and 0.004), while for FEV_1/FVC the interaction was significant for early menopause (p=0.04) and borderline for late menopause (p=0.07). In the subgroup analyses based on median BMI, the interaction was significant for FEV_1/FVC for both early and late menopause ($p=4.6 \times 10^{-7}$ and 0.005). For airflow obstruction, the interaction was significant for early (p=0.026) and borderline for late menopause (p=0.07).

Observational analyses

In the observational analyses, early menopause showed statistically significant lower FEV_1 (-31.4mL [-42.0 to -20.9]), lower FVC (-36.3mL [-48.8 to -23.8]) and a higher risk of spirometric restriction (OR 1.13 [1.02 to 1.24]) (Figure 2 and Table S3). Early menopause was also associated with lower FEV_1/FVC, although the confidence interval was very large (-0.19% [-0.34 to -0.03]), and possibly a higher risk of airflow obstruction (OR 1.09 [1.00 to 1.19]) that did not reach statistical significance. Late menopause was not associated with any of the five lung function outcomes.

Discussion

Contrary to observational findings, our MR study suggests that early menopause has a protective effect on airflow obstruction, with no clear evidence of an effect on FVC or spirometric restriction.[5, 31–35] We found a 15% decrease in the risk of airflow obstruction for women with menopause before the age of 45 compared to women with a normal age at menopause, and this protective effect was less strong in women who had used HRT as well as in overweight women. Although there was some evidence of pleiotropy, overall our findings were consistent when using MR methods robust to pleiotropy.

MR studies can be considered similar to randomized controlled trials (RCTs) in that exposure to a specific genetic variant is assigned randomly at conception. MR estimates are therefore not affected by classical confounding factors. However, MR studies can provide evidence of a causal effect only if the three key assumptions underlying MR hold (Figure 1).[36, 37] The first assumption (relevance assumption) is that the SNPs used as instruments are associated with menopause, and we have strengthen this by removing weak instruments (F statistic <10). The second assumption (independence assumption), is that the association between the SNP and the outcome is not confounded and the third, and most important assumption (exclusion restriction) is the absence of pleiotropy, i.e. the SNP is not associated with other traits that independently affect the outcome. Related to assumption 2, the main confounder for genetic associations is population stratification, and we have addressed this by adjusting for ancestry principal components. The impact of violations of assumptions 2 and 3 can be assessed by excluding SNPs known to be associated with traits that could affect lung function. We *a priori* considered height, BMI, and age at menarche as potential sources of confounding and/or pleiotropy because these traits are associated with lung function, and 25%, 8% and 6% respectively of the 63 included SNPs have been previously associated with these traits. Removing these SNPs resulted in similar results to those of the main analyses, suggesting no major impact on the MR results through genetic associations of these traits. The presence of pleiotropy can also be investigated by looking at the variation between MR estimates from the individual SNPs. We would expect the individual MR estimates to vary only by chance if all included SNPs were valid instruments (i.e. no pleiotropy).[22] There was a suggestion of pleiotropy in our main analyses on FEV_1/FVC, FVC, and airflow obstruction (I^2: 16-48), but not for spirometric restriction (I^2= 0). However, when we excluded possible pleiotropic SNPs, there was still residual heterogeneity (I^2: 2-57), which could be due to other (unknown) independent pathways. It is important to note that I^2 is not independent of sample size or number of instruments, and with large sample sizes high I^2 values might be observed in the absence of pleiotropy.[22] The consistency between the findings of the different MR methods provides reassurance and indicates the robustness of our findings related to airflow obstruction.

Our findings when using age at menopause as a continuous variable were consistent with those for early and late menopause. Of note, this MR analysis had 90% power to detect a minimum difference in FVC of 6.4ml per year increase in age at menopause, and hence we cannot exclude a smaller effect of age at menopause on FVC.[38] Our main analyses suggested the possibility of a small detrimental effect of early menopause on FVC (-5mL; p=0.08). When we excluded possible pleiotropic SNPs, this association became significant (p=0.03) and its direction was the same as in the observational analysis, although of much smaller magnitude (-6.7mL vs. -36mL). We thus cannot confirm the detrimental effect of early menopause on FVC found in observational analyses, but if there is a true causal effect this is likely to be small.

Most observational studies reported lower FEV_1 and FVC in post-menopausal women compared to pre-menopausal, but no effect on FEV_1/FVC or airflow obstruction.[5, 31–35] Amaral et al. studied the effect of age at menopause (categorized in five groups) on lung function in the UKB and found that an earlier age at menopause associated with lower FVC and FEV_1, and with a higher risk of spirometric restriction.[5] In line with this study, but focusing on early and late menopause and adjusting for additional potential confounders, our observational analysis in UKB showed strong associations of early menopause with lower FVC and a 13% higher risk of spirometric restriction. Based on the same UKB study population but using MR, we found strong associations of early menopause with higher FEV_1/FVC and a 15% lower risk of airflow obstruction. We could not confirm a strong effect on FVC nor spirometric restriction using MR. A reason why we find a protective effect of early menopause on airflow obstruction in MR that we do not find in observational studies might be confounding of the observational findings by factors that increase the risk of early menopause and decrease lung function, which could include early life factors, diet, and occupational exposures. Confounding might also explain why early menopause is associated with a stronger reduction in FVC in observational analyses compared to MR. Future studies that can account for more potential confounders could help explain the inconsistency between observational and MR findings.

Menopause marks the end of the reproductive period, which is defined as the time between menarche and menopause, and in fact age at menopause was highly correlated with the length of the reproductive period in our data (correlation coefficient of 0.93). Early menopause might thus reflect the effect of a shorter lifetime "exposure" to female sex hormones. We would expect less of an effect of early menopause on airflow obstruction in women who still have high levels of female sex hormones after menopause, including women taking hormonal therapies and obese women with higher endogenous levels. We therefore performed subgroup analyses by MHT use and by BMI, and found that the effect of early menopause on airflow obstruction was not so apparent in these groups, supporting this hypothesis. The role of sex hormones in the lung is complex and there are biological reasons to support either a beneficial or a detrimental effect depending on the type of hormone, concentration, duration of exposure, cell type, and their interactions.[2, 39] Beneficial effects of hormone therapy on lung function after 3-6 months MHT use were reported by small RCTs, while a crossover RCT reported no improvement in lung function after MHT use.[40–43] Previous research in mice has shown that oestrogens may potentiate the oxidative stress after smoking exposure, and thereby contribute to airway remodelling.[29] We therefore performed subgroup analyses by smoking status, but found no evidence of a difference between smokers and non-smokers.

Although, technically the reproductive period is also defined by menarche, age at menarche varies very little compared to age at menopause and therefore influences lifetime exposure to sex hormones to a much lesser extent than age at menopause. Interestingly, an earlier age at menarche has been associated with a reduced FVC in adult women in a previous MR study, while no association was found for FEV_1/FVC.[38] The proposed mechanism for the effect of early menarche relates to premature completion of lung development and a lower maximal attained lung function, which has been confirmed by an observational longitudinal study.[44] Therefore the effect of age at menarche on lung function might not be through sex hormones, unlike what we hypothesise for age at menopause.

A limitation of our study is the use of self-reported information on age at menopause. However, the misclassification is likely to be random and the measurement error would reduce power rather than causing bias. UKB did not perform post-bronchodilator pulmonary function measurements, so we cannot distinguish between reversible and fixed airflow obstruction. When we excluded self-reported asthmatics from the MR analyses, we found almost identical results compared to the main analysis.

Strengths of our study are the large sample size, which is needed for MR, and the 6% variance explained in age at menopause by the SNPs used in our MR, which is relatively high.

In conclusion, this MR study suggests that the earlier a woman's menopause, the less likely she is to have airflow obstruction. Future research is needed to further assess the effect of female sex hormones and the length of the reproductive period on lung function. In addition, our MR study could not confirm a strong effect of early menopause on FVC and spirometric restriction as found in observational studies, and further work might explain this inconsistency.

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Table 1. Characteristics of the study population.

	Women included in MR (N=94,742)	Women with complete data† (N=84,844)	Women with early menopause (N=7,206)	Women with late menopause (N=8,468)
Age (years)	60 (5.3)	60 (5.3)	59 (6.8)	62 (3.4)
Height (cm)	162 (6.1)	162 (6.1)	162 (6.2)	162 (6.0)
BMI (kg/m^2)	26.9 (4.9)	26.8 (4.8)	27.0 (5.0)	27.5 (5.0)
Age at menopause (years)	51 (4.0)	51 (4.0)	42 (1.4)	57 (1.2)
Early menopause (<45 years)	7,206 (7.6%)	6,369 (7.5%)	7,206 (100%)	-
Late menopause (>55 years)	8,468 (8.9%)	7,541 (8.9%)	-	8,468 (100%)
Age at menarche (years)	13 (1.6)	13 (1.6)	13 (2.9)	13 (2.4)
Lung function				
FVC%pred (%)	97.4 (15.7)	97.7 (15.6)	95.7 (15.9)	97.5 (15.6)
FEV_1%pred (%)	93.1 (16.8)	93.4 (16.7)	91.1 (17.3)	93.3 (16.8)
FEV_1/FVC (%)	75.3 (6.3)	75.3 (6.3)	75.1 (6.7)	75.2 (6.3)
FEV_1/FVC < LLN (N)	7,979 (8.4%)	7,010 (8.3%)	727 (10%)	637 (7.5%)
FVC < LLN (N)	6,869 (7.3%)	5,892 (6.9%)	650 (9.0%)	585 (6.9%)
Asthma*	10,900 (12%)	9,726 (11%)	926 (13%)	993 (12%)
Smoking status				
Never-smoker	53,831 (57%)	48,393 (57%)	3,633 (50%)	4,995 (59%)
Ex-smoker	33,518 (35%)	30,194 (36%)	2,685 (37%)	3,016 (36%)
Current-smoker	7,370 (8%)	6,257 (7%)	884 (12%)	455 (5%)
Pack-years in smokers	21 (16)	20 (15)	24 (16)	20 (16)
Menopausal Hormone Therapy (MHT)				
Never used	53,946 (57%)	48,395 (57%)	3,201 (45%)	4,390 (52%)
Ex-user	36,261 (38%)	32,407 (38%)	3,459 (48%)	3,739 (44%)
Current user	4,375 (5%)	4,042 (5%)	532 (7%)	328 (4%)

Values reported are mean (standard deviation) or N (%).

See Supplementary table S1 for more variables and subgroups.

**Self-reported doctor diagnosed asthma ever.*

†*Women with complete data on all variables included in the observational analyses.*

Table 2. Association of early menopause with airflow obstruction in observational and MR analyses.

		N	*FEV_1/FVC (%)*				*FEV_1/FVC < LLN*			
	N	**SNPs**	**B**	**95%CI**	**P**	**I^2**	**OR**	**95%CI**	**P**	**I^2**
Observational analysis	77,303	-	-0.19	-0.34 to -0.03	**0.019**	NA	1.09	1.00 to 1.19	0.063	NA
Main MR analysis (All SNPs)	86,274	39	0.29	0.22 to 0.36	**$1.48x10^{-16}$**	48 [34-83]	0.85	0.82 to 0.89	**$5.88x10^{-14}$**	16 [0-60]
Exclusion of pleiotropic SNPs										
Height SNPs excluded	86,274	30	0.28	0.21 to 0.36	**$2.29x10^{-13}$**	56 [47-88]	0.84	0.81 to 0.88	**$1.44x10^{-13}$**	26 [0-70]
BMI SNPs excluded	86,274	36	0.29	0.22 to 0.36	**$1.93x10^{-16}$**	55 [39-85]	0.85	0.82 to 0.89	**$7.60x10^{-14}$**	19 [0-64]
Menarche SNPs excluded	86,274	36	0.29	0.22 to 0.36	**$1.02x10^{-14}$**	49 [34-84]	0.84	0.81 to 0.88	**$2.85x10^{-14}$**	19 [0-63]
All pleiotropic SNPs excluded*	86,274	28	0.29	0.22 to 0.37	**$7.13x10^{-14}$**	57 [49-89]	0.84	0.80 to 0.88	**$1.19x10^{-13}$**	30 [0-74]
Sensitivity MR analyses										
Women with complete data†	77,303	39	0.28	0.21 to 0.35	**$1.86x10^{-14}$**	45 [25-80]	0.87	0.84 to 0.91	**$7.14x10^{-10}$**	14 [0-58]
Non-asthmatic women	76,367	39	0.31	0.24 to 0.38	**$7.47x10^{-18}$**	42 [19-80]	0.84	0.80 to 0.88	**$2.07x10^{-12}$**	7 [0-48]
Limiting to Day *et al.* SNPs	86,274	33	0.29	0.18 to 0.39	**$3.75x10^{-8}$**	38 [5-77]	0.89	0.84 to 0.95	**$2.20x10^{-4}$**	4 [0-54]

** All pleiotropic SNPs include all SNPs associated with height, BMI and menarche. SNPs associated with the traits were selected based on the results from the Phenoscanner with a $p<7.94x10^{-4}$ (0.05/63).*

†Women with complete data on all variables included in the observational analyses.

LLN = Lower Limit of Normal, N = number of subjects included in analysis, N SNPs = number SNPs included in analysis, B = beta, 95%CI = 95% Confidence Interval, P = P-value, I^2 = between-instrument heterogeneity indicator, OR = Odds Ratio, and NA = Not applicable. Significant results are show in bold.

Table 3. Association of late menopause with airflow obstruction in observational and MR analyses

	N	N SNPs	*FEV_1/FVC (%)* B	95%CI	P	I^2	*FEV_1/FVC < LLN* OR	95%CI	P	I^2
Observational analysis	78,475	-	0.11	-0.04 to 0.25	0.139	NA	0.92	0.84 to 1.02	0.101	NA
Main MR analysis (All SNPs)	87,536	40	-0.18	-0.26 to -0.10	**1.09×10^{-5}**	53 [44-84]	1.06	1.01 to 1.11	**0.018**	20 [0-58]
Exclusion of pleiotropic SNPs										
Height SNPs excluded	87,536	31	-0.22	-0.33 to -0.11	**6.90×10^{-5}**	61 [49-86]	1.10	1.03 to 1.17	**4.53×10^{-3}**	23 [0-60]
BMI SNPs excluded	87,536	37	-0.17	-0.26 to -0.09	**3.13×10^{-5}**	54 [44-85]	1.06	1.01 to 1.11	**0.027**	20 [0-59]
Menarche SNPs excluded	87,536	37	-0.23	-0.33 to -0.13	**7.32×10^{-6}**	56 [43-83]	1.11	1.04 to 1.17	**1.09×10^{-3}**	24 [0-57]
All pleiotropic SNPs excluded*	87,536	28	-0.22	-0.33 to -0.11	**1.33×10^{-4}**	61 [49-87]	1.09	1.02 to 1.17	**0.015**	23 [0-61]
Sensitivity MR analyses										
Women with complete data†	78,475	40	-0.17	-0.25 to -0.08	**9.63×10^{-5}**	53 [44-84]	1.05	1.00 to 1.11	**0.042**	13 [0-51]
Non-asthmatic women	77,562	40	-0.18	-0.26 to -0.10	**1.79×10^{-5}**	53 [44-83]	1.06	1.00 to 1.12	**0.044**	6 [0-48]
Limiting to Day *et al.* SNPs	87,536	33	-0.17	-0.27 to -0.08	**4.39×10^{-4}**	44 [20-83]	1.05	0.99 to 1.12	0.077	6 [0-52]

** All pleiotropic SNPs include all SNPs associated with height, BMI and menarche. SNPs associated with the traits were selected based on the results from the Phenoscanner with a $p<7.94 \times 10^{-4}$ (0.05/63).*

†Women with complete data on all variables included in the observational analyses.

LLN = Lower Limit of Normal, N = number of subjects included in analysis, N SNPs = number SNPs included in analysis, B = beta, 95%CI = 95% Confidence Interval, P = P-value, I^2 = between-instrument heterogeneity indicator, OR = Odds Ratio, and NA = Not applicable. Significant results are show in bold.

Figure legends

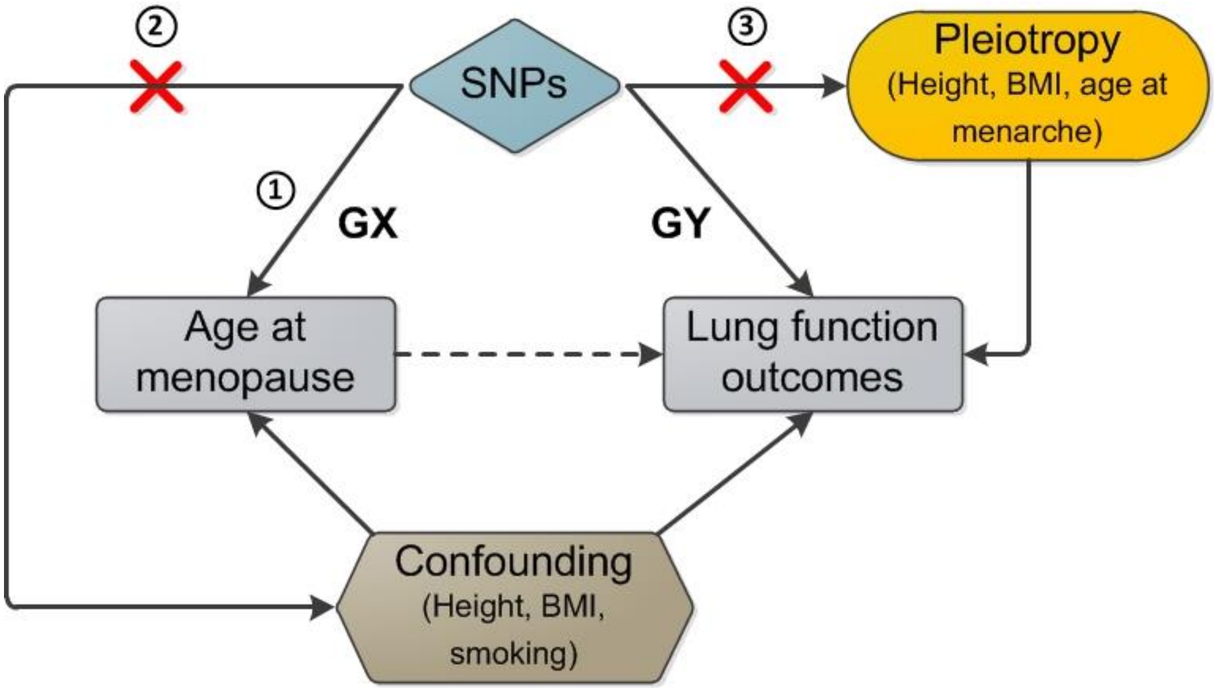
Figure 1. **Schematic overview of Mendelian Randomization.**

For each SNP, the MR effect estimate is calculated using the GX and GY associations. MR assumptions: 1) Relevance assumption: SNPs are associated with exposure (age at menopause); 2) Independent assumption: the association between SNP and outcome is NOT confounded; and 3) Exclusion restriction assumption: SNPs affect outcome (lung function) only through the exposure and NOT through independent pathways (i.e. absence of pleiotropy).

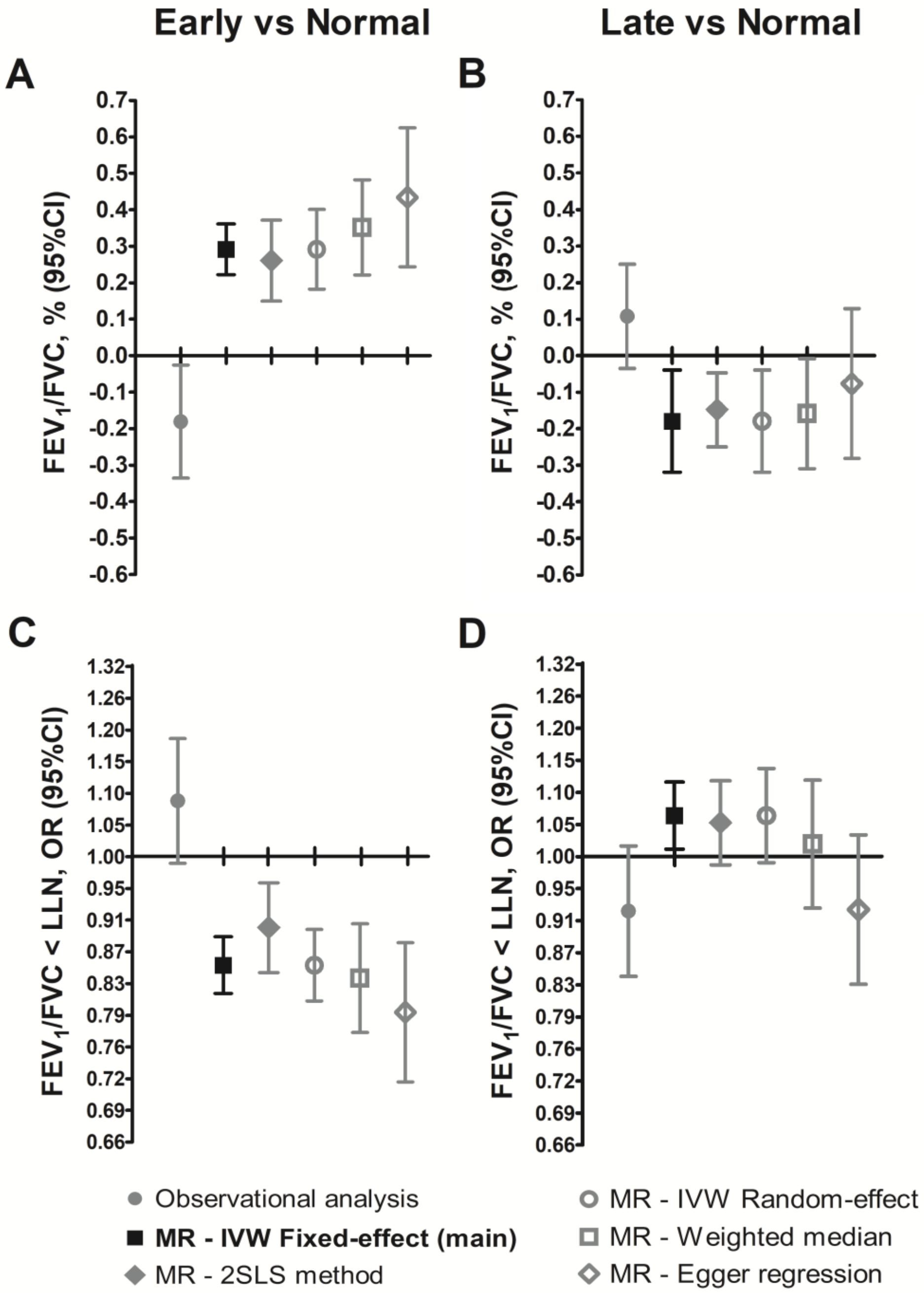
Figure 2. Association of early and late menopause with airflow obstruction in observational and MR analyses. Early menopause: A) FEV_1/FVC and C) FEV_1/FVC <LLN; Late menopause: B) FEV_1/FVC and D) FEV_1/FVC <LLN.

The observational analyses (linear/logistic regression) were adjusted for age, age2, height, centre, BMI, smoking groups, Townsend deprivation index, level of education, physical activity, number of live births, age at menarche, ever oral contraceptive use, and use of MHT. All MR analyses were adjusted for: age, age2, height, centre, first 10 principal components, and genotyping batch. IVW = inverse variance-weighted average method; 2SLS = Two-Stage Least Squares regression. For MR-PRESSO, both unadjusted analyses (raw) and analyses after removal of outliers if any were detected (corrected) are shown.

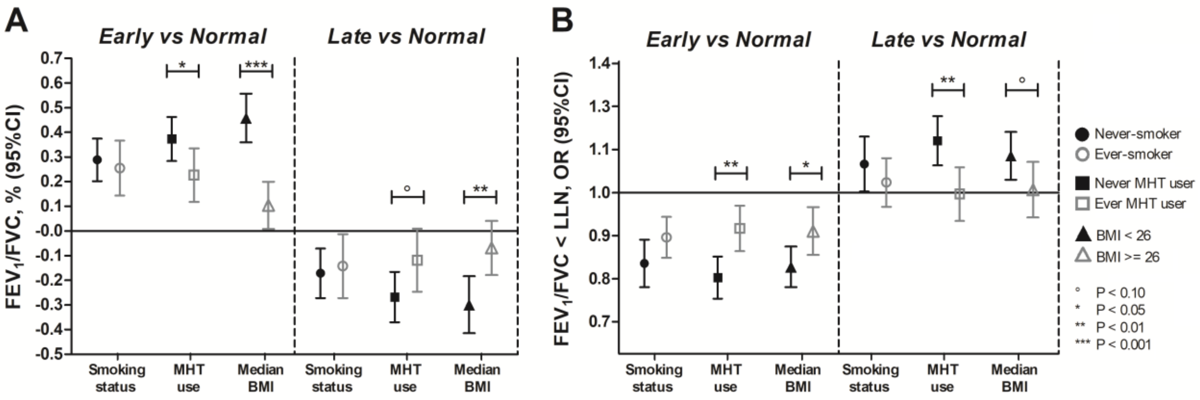
Figure 3. MR estimates of the effect of age at menopause on A) FEV_1/FVC and B) airflow obstruction in subgroup analyses by smoking status, MHT use and current BMI.



②
SNPs
③
Pleiotropy
(Height, BMI, age at menarche)
①
GX
GY
Age at menopause
Lung function outcomes
Confounding
(Height, BMI, smoking)



Early vs Normal
Late vs Normal
A
B
C
D
FEV1/FVC, % (95%CI)
FEV1/FVC < LLN, OR (95%CI)
Observational analysis
MR - IVW Fixed-effect (main)
MR - 2SLS method
MR - IVW Random-effect
MR - Weighted median
MR - Egger regression


A
Early vs Normal
Late vs Normal
FEV1/FVC, % (95%CI)
Smoking status
MHT use
Median BMI
B
FEV1/FVC < LLN, OR (95%CI)
Never-smoker
Ever-smoker
Never MHT user
Ever MHT user
BMI < 26
BMI >= 26
° P < 0.10
* P < 0.05
** P < 0.01
*** P < 0.001

Supplementary material

Age at menopause and lung function: a Mendelian Randomization study

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Supplementary Methods

Study population

We analysed post-menopausal women with a white ethnic background recruited in 2006–2010 from the UK Biobank. The UK Biobank is a very large, publicly available, population-based prospective study with over 500,000 participants aged 39-70 divided over 22 study centres across the United Kingdom.[1] It was established aiming to identify and understand the (genetic or non-genetic) determinants of chronic disease in middle-aged and elderly adults. All participants provided written consent, completed online questionnaires and most underwent physical measurements, including spirometry using a Vitalograph Pneumotrac 6800 spirometer (post-bronchodilator measurements were not performed).[2] The UK National Research Ethics Service Committee North West (Haydock) approved the study. Details on genotyping and imputation methods and quality control procedures in the UK Biobank are available elsewhere.[3]

Age at natural menopause was based on self-reported answers on the questions: "Have you had your menopause (periods stopped)?" and "How old were you when your periods stopped?". We excluded from the study women with surgical menopause (woman who had an oophorectomy and/or hysterectomy, unless surgery was after their reported age at menopause). This was based on the questions: "Have you had both ovaries removed?" and "Have you had a hysterectomy (womb removed)?". Furthermore, we also excluded: women with extreme age at menopause, i.e. <40 years (1% of the sample) or >60 years (99%); women with lung function levels outside the limits set by the Global Lung Function Initiative 2012 (GLI-2012)[4] to be able to calculate the lower limit of normal values (LLN); women who used an inhaler before spirometry; and close relatives (first degree). See figure E1 for the complete flow diagram of subject selection. We categorized age at menopause as early (<45 years), normal (45 to 55), or late (>55), using normal as the reference category in the analyses.

Lung function outcomes

We investigated the continuous outcomes (pre-bronchodilator) forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC and, as well as the binary outcomes airflow obstruction, defined as FEV_1/FVC< LLN, and spirometric restriction, defined as FVC<LLN. The LLN was based on GLI-2012.[4] We used spirometry data that passed the best measure criteria as developed by the UK BiLEVE study along with the ERS/ATS spirometry guidelines.[5, 6]

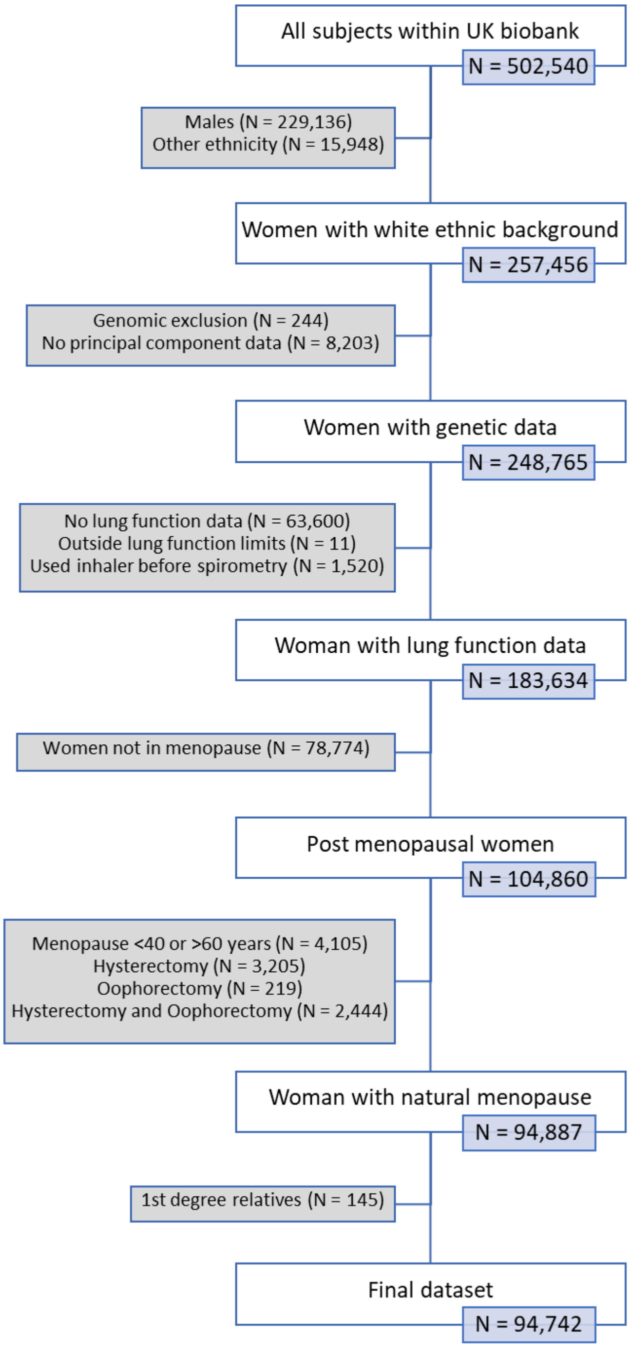

Figure E1. Flow diagram of subject selection.

Choice of instruments for MR analyses

A literature search was performed to find genome-wide association studies (GWAS) on age at natural menopause. Both the GWAS catalogue [7] and GWAS central [8] were consulted, and references and citations were checked for additional studies. All SNPs associated with age at menopause and the genome-wide threshold level of $5x10^{-8}$ from the most recent paper by Day et al. were selected (n=57).[9] This list was supplemented with SNPs associated with age at menopause at genome-wide level from the previous GWASs, including Stolk *et al.* 2012 (n=11), Stolk *et al.* 2009 (n=2), He *et al.* 2009 (n=9), and Lunetta *et al.* 2007 (n=1).[10–13] In total, 80 SNPs were identified. Genetic data was available in UK Biobank for all SNPs, with one exception (rs148126992). Based on UK biobank data, we calculated the correlation between SNPs (r^2) and the F-statistic per SNP for the association with early, late and continuous age at menopause. The F-statistic reflects the strength of the association between the SNP and age at menopause, and a value of 10 ($F<10$) is a widely used arbitrary threshold for weak instruments. By keeping only SNPs that were strong instruments ($F>10$) to avoid weak instrument bias and that were not highly correlated with each other ($r^2<0.8$), 63 SNPs remained that jointly explained 6% of the UKB population variance of age at menopause.[14] Of these, 39 SNPs were strong instruments for early menopause and 40 for late menopause. All SNPs had good imputation quality (info score>0.96).

MR analyses

As our main analysis, we estimated the causal effect of early (< 45 years) and late (> 55) menopause compared to a normal age at menopause (45 - 55) on lung function, but we also performed MR analyses considering age at menopause as a continuous variable as secondary analyses.

For each of the included SNPs we obtained two estimates, one for the association between the SNP with early/late menopause (GX) and one for the association with the lung function outcome (GY) (Figure 1). We performed logistic regression analyses between the SNPs and either early vs normal or late vs normal menopause to obtain the GX estimates; and we performed either linear (FEV_1/FVC, FVC, and FEV_1) or logistic (airway obstruction and spirometric restriction) regression analyses of the SNPs and the five lung function outcomes to obtain the GY estimates. Both associations (GX and GY) were adjusted for centre, first 10 ancestry principal components and thee genotyping batches (The first batch genotyped using the UK BiLEVE array and the second and third batch genotyped using the UK Biobank Axiom array but released at two time points). The GY association was additionally adjusted for age, age^2 and height. For each SNP, an MR estimate was derived as the ratio of GY over GX (Wald estimator) and its standard error obtained using the Delta method.[15] SNP-specific MR estimates were then pooled using an inverse-variance weighted (IVW) fixed-effect meta-analysis method that accounts for correlation between SNPs (R package *MendelianRandomization*).[14, 16] This allows for correlated SNPs ($0 < r^2 < 0.8$) to be included in the MR analysis, which may increase the power of the analysis. We used the IVW two-sample MR method because the standard MR approach in a one-sample setting (as in our study), which is the two-stage least square (2SLS) method, does not account for pleiotropy.

<u>Assessing pleiotropy</u>

There is pleiotropy if a SNP is associated with other traits that independently affect the outcome (lung function).[17] As a proxy for the presence of pleiotropy, we assessed the between-instrument heterogeneity of the MR estimates in the IVW-analysis, using the I^2 statistic and the Q test p-value.[18] The Q statistic was obtained from the *MendelianRandomization* R package, and the I^2 was estimated using the *metafor* R package.

To further investigated pleiotropy, we performed sensitivity analyses using other MR methods robust to pleiotropy based on different assumptions about the direction of possible pleiotropic effects: 1) IVW random-effect meta-analysis (IVW-R, assumes random pleiotropic effects); 2) weighted median analysis (assumes that at least 50% of the SNPs are valid IVs with no assumption on the direction of pleiotropic effects); 3) MR-Egger regression with penalized weight (assumes directional pleiotropic effects); 4) MR-PRESSO (corrects for horizontal pleiotropy by removing pleiotropic outlier SNPs).[19–22] For MR-Egger, we assessed the "NO Measurement Error" (NOME) assumption by estimating the variability in GX estimates using the I^2_{GX} [23]; if the I^2_{GX} is less than 90%, results from MR-Egger should be interpreted with caution. In our study the I^2_{GX} is 98% for both early and late menopause.

Furthermore, we *a priori* considered height, BMI, and age at menarche as potential sources of pleiotropy. We searched the literature to assess if the menopause SNPs were also associated with these traits using the online application PhenoScanner.[24] Menopause SNPs that were associated with these traits at a p-value threshold of 7.94×10^{-4} (Bonferroni correction, 0.05/63) were excluded in sensitivity analyses.

All analyses were performed using R (version 3.4.1). In particular, the IVW and MR-Egger analyses were performed using the *MendelianRandomization* package which uses a (Pearson) correlation matrix to adjust for correlation between SNPs, the weighted median analyses using the *metafor* package, and the 2SLS analyses were carried out using the *stats* package performing two separate regression analyses for step one and two.[16]

Sensitivity analyses

We performed several sensitivity analyses to assess the robustness of our findings to choices made *a priori* for our MR analyses. These relate to the MR method used, the sample used, and the choice of SNPs used as instruments. First, we performed the standard MR approach in a one-sample setting (as in the current study): the two-stage least square (2SLS) regression analysis, which assumes no pleiotropy similarly to the IVW fixed-effect method. In 2SLS, first the risk factor (menopause) is regressed jointly on all SNPs and second the outcome (lung function) is regressed on the predicted values of the risk factor from the first regression.[25] However, using the 2SLS method it is not possible to assess the level of heterogeneity, and thus pleiotropy, and therefore we used the two-sample MR method in our main MR analyses. Second, we restricted the main MR analysis to exactly the same number of women included in the observational analysis to allow comparison between the two approaches (n=84,844). Third, since no post-bronchodilator measurements were performed in UK biobank, we also repeated the MR analyses in non-asthmatics based on self-reported doctor diagnosed asthma as these women may have reversible airflow obstruction. Fourth, we limited the MR analyses to the 54 SNPs identified by the most recent and largest GWAS on age at menopause (Day *et al*. [9]) and did not adjust for correlation (the 54 SNPs are independent) or remove weak SNPs in these analyses. Finally, we used the GX estimate for continuous age at menopause from the literature (Day et al. [9]) and the GY from UKB to further investigate the robustness of our findings when using two independent data sources (two-sample MR) instead of a single dataset (one-sample MR).

Subgroup analyses

To investigate potential effect modification, we performed subgroup analyses based on smoking status (never/ever-smokers), MHT use (never/ever-MHT user), and current BMI (low vs. high, based on median value of 26kg/m²). First, previous research reported that a longer exposure to female sex hormones may increase susceptibility to smoking effects [26, 27]. Secondly, we hypothesized that the protective effect of an earlier age at menopause reflects the effect of a shorter exposure to oestrogens, and thus no effect of age at menopause on lung function would be observed in women who are still exposed to oestrogens after menopause. This could be the case for women using MHT and in obese women since androgens are converted into oestrogens in adipose tissues. An interaction p-value was calculated by computing a z-score using the effect estimate and standard error of both subgroup analyses. This corresponds to a p-value obtained using an interaction term in the analyses, which is not possible in MR.

Observational analyses

Earlier observational analysis in UK Biobank examined age at menopause as a categorical variable divided into five groups.[2] For comparison with our MR findings, we repeated these regression analyses yet using early/normal/late menopause and including more confounders. Included confounders were those in the previous analyses: centre, age, age^2, height, body-mass index (BMI:<18.5; 18.5-25; 25-30; >30), smoking groups (never-smoker; never-smoker exposed to passive smoke; ex-smoker with <15 pack-years (py); ex-smoker with ≥15 py; current-smoker with <15 py; current-smoker with ≥15 py; ex- and current-smokers with unknown py), Townsend deprivation index, Menopausal Hormone Therapy use (MHT: never, ex, current), number of live births (n=0,1,2,3,≥4), oral contraceptive ever use, and age at menarche; supplemented with: education level (high school; college; university; unknown) and physical activity (moderate (≥2 hours week); vigorous (≥2 hours week)). In addition, smoking groups were used in the current analysis instead of including smoking status and pack-years (continuous) separately as done earlier.[2]

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Supplementary tables

Table S1_A: Characteristics of the study population divided into subgroups.
*Values reported are mean (standard deviation) or N (%). *Women with complete data on all variables included in the observational analyses.*

	Women included in MR (N=94,742)	*Women with complete data* (N=84,844)*	*Women with missing data on confounders (N=9,898)*
Age (years)	60 (5.3)	60 (5.3)	61 (5.3)
Height (cm)	162 (6.1)	162 (6.1)	161 (6.2)
BMI (kg/m^2)	26.9 (4.9)	26.8 (4.8)	27.9 (5.3)
Underweight (<18.5)	573 (0.6%)	524 (0.6%)	49 (0.005%)
Normal (18.5-25)	37,616 (40%)	34,449 (41%)	3167 (32%)
Overweight (25-30)	36,288 (38%)	32,464 (38%)	3824 (39%)
Obese (>30)	20,186 (21%)	17,407 (21%)	2779 (28%)
Age at menopause (years)	51 (4.0)	51 (4.0)	50 (4.1)
Early menopause (<45 years)	7,206 (7.6%)	6,369 (7.5%)	837 (8.5%)
Late menopause (>55 years)	8,468 (8.9%)	7,541 (8.9%)	927 (9.4%)
Age at menarche (years)	13 (1.6)	13 (1.6)	10 (5.8)
Lung function outcomes			
FVC%pred (%)	97.4 (15.7)	97.7 (15.6)	95.5 (16.4)
FEV_1%pred (%)	93.1 (16.8)	93.4 (16.7)	90.9 (17.5)
FEV_1/FVC (%)	75.3 (6.3)	75.3 (6.3)	74.9 (6.6)
FEV_1/FVC < LLN (N)	7,979 (8.4%)	7,010 (8.3%)	969 (9.8%)
FVC < LLN (N)	6,869 (7.3%)	5,892 (6.9%)	977 (9.9%)
Self-reported asthma (N)	10,900 (11.5%)	9,726 (11.4%)	1,174 (11.9%)
Smoking status			
Never-smoker	53,831 (57%)	48,393 (57%)	5,438 (55%)
Ex-smoker	33,518 (35%)	30,194 (36%)	3,324 (34%)
Current-smoker	7,370 (8%)	6,257 (7%)	1,113 (11%)
Pack-years in smokers	21 (16)	20 (15)	24 (17)
Menopausal Hormone Therapy use (MHT)			
Never used	53,946 (57%)	48,395 (57%)	5,551 (57%)
Ex-user	36,261 (38%)	32,407 (38%)	3,854 (40%)
Current user	4,375 (5%)	4,042 (5%)	333 (3%)
Oral contraceptive use ever	75,599 (80%)	68,326 (81%)	7,273 (74%)
Townsend deprivation index	-1.66 (2.85)	-1.71 (2.82)	-1.23 (3.09)
Education level			
Low (High school)	41,603 (44%)	35,486 (42%)	6,120 (62%)
Medium (College)	15,346 (16%)	13,956 (16%)	1,390 (14%)
High (University)	36,906 (39%)	34,757 (41%)	2,149 (22%)
Physical activity			
Moderate	75,531 (82%)	69,140 (82%)	4,391 (88%)
Vigorous	41,147 (46%)	39,397 (46%)	1,750 (33%)
Live births			
0	15,484 (16%)	14,062 (17%)	1,422 (14%)
1	11,867 (13%)	10,565 (12%)	1,302 (13%)
2	44,096 (47%)	39,560 (47%)	4,536 (46%)
3	17,570 (19%)	15,727 (19%)	1,843 (19%)
>4	5,686 (6%)	4,930 (6%)	756 (8%)

Table S1_B: Characteristics of the study population divided into subgroups.
*Values reported are mean (standard deviation) or N (%). *Women with complete data on all variables included in the observational analyses.*

	Women with early menopause (N=7,206)	*Women with late menopause (N=8,468)*	*Never MHT users (N=53,946)*	*Ever MHT users (N=40,636)*
Age (years)	59 (6.8)	63 (3.4)	59 (5.5)	61 (4.8)
Height (cm)	162 (6.2)	162 (6.0)	162 (6.1)	162 (6.1)
BMI (kg/m^2)	27.0 (5.0)	27.5 (5.0)	26.9 (5.0)	26.8 (4.7)
Underweight (<18.5)	60 (0.8%)	39 (0.5%)	364 (0.7%)	208 (0.5%)
Normal (18.5-25)	2,737 (38%)	2,883 (34%)	21,678 (40%)	15,884 (39%)
Overweight (25-30)	2,766 (38%)	3,400 (40%)	20,126 (37%)	16,105 (40%)
Obese (>30)	1,636 (23%)	2,139 (25%)	11,737 (22%)	8,401 (21%)
Age at menopause (years)	42 (1.4)	57 (1.2)	51 (3.7)	50 (4.3)
Early menopause (<45 years)	7,206 (100%)	-	3,201 (5.9%)	3,991 (9.8%)
Late menopause (>55 years)	-	8,468 (100%)	4,390 (8.1%)	4,067 (10%)
Age at menarche (years)	13 (2.9)	13 (2.4)	13 (2.6)	13 (1.6)
Lung function outcomes				
FVC%pred (%)	95.7 (15.9)	97.5 (15.6)	97.6 (15.6)	97.2 (15.8)
FEV_1%pred (%)	91.1 (17.3)	93.3 (16.8)	93.5 (16.5)	92.6 (17.1)
FEV_1/FVC (%)	75.1 (6.7)	75.2 (6.3)	75.7 (6.2)	74.9 (6.5)
FEV_1/FVC < LLN (N)	727 (10%)	637 (7.5%)	4,196 (7.8%)	3,763 (9.3%)
FVC < LLN (N)	650 (9.0%)	585 (6.9%)	3,879 (7.2%)	2,967 (7.3%)
Self-reported asthma (N)	926 (12.9%)	993 (11.7%)	5,698 (10.6%)	2,186 (12.6%)
Smoking status				
Never-smoker	3,633 (50%)	4,995 (59%)	32,705 (61%)	21,042 (52%)
Ex-smoker	2,685 (37%)	3,016 (36%)	17,331 (32%)	16,133 (40%)
Current-smoker	884 (12%)	455 (5%)	3,898 (7%)	3,450 (8%)
Pack-years in smokers	24 (16)	20 (16)	20 (15)	22 (16)
Menopausal Hormone Therapy use (MHT)				
Never used	3,201 (45%)	4,390 (52%)	53,946 (100%)	-
Ex-user	3,459 (48%)	3,739 (44%)	-	36,261 (89%)
Current user	532 (7%)	328 (4%)	-	4,375 (11%)
Oral contraceptive use ever	5,796 (81%)	6,545 (76%)	42,011 (78%)	33,472 (82%)
Townsend deprivation index	-1.36 (3.03)	-1.78 (2.79)	-1.68 (2.83)	-1.64 (2.87)
Education level				
Low (High school)	3,539 (49%)	3,972 (47%)	22,192 (41%)	19,339 (48%)
Medium (College)	1,179 (16%)	1,298 (15%)	8,918 (17%)	6,405 (16%)
High (University)	2,387 (33%)	3,122 (37%)	22,345 (41%)	14,500 (36%)
Physical activity				
Moderate	5,529 (81%)	6,667 (84%)	41,678 (81%)	31,743 (82%)
Vigorous	3,076 (45%)	3,696 (46%)	23,182 (45%)	17,912 (46%)
Live births				
0	1,445 (20%)	965 (11%)	9,392 (17%)	6,069 (15%)
1	1,030 (14%)	967 (11%)	6,622 (12%)	5,222 (13%)
2	3,049 (42%)	4,141 (49%)	24,866 (46%)	19,170 (47%)
3	1,231 (17%)	1,760 (21%)	9,857 (18%)	7,681 (19%)
>4	450 (6%)	629 (7%)	3,187 (6%)	2,478 (6%)

Table S1_C: Characteristics of the study population divided into subgroups.
*Values reported are mean (standard deviation) or N (%). *Women with complete data on all variables included in the observational analyses.*

	Never-smokers (N=53,831)	*Ever-smokers (N=40,888)*	*BMI < 26 (N=47,328)*	*BMI >= 26 (N=47,335)*
Age (years)	60 (5.3)	60 (5.3)	60 (5.3)	60 (5.3)
Height (cm)	162 (6.1)	162 (6.1)	163 (6.1)	162 (6.1)
BMI (kg/m^2)	26.7 (4.8)	27.1 (4.9)	23.2 (1.9)	30.5 (4.2)
Underweight (<18.5)	323 (0.6%)	249 (0.6%)	573 (1.2%)	-
Normal (18.5-25)	22,245 (41%)	15,358 (38%)	37,616 (79%)	-
Overweight (25-30)	20,188 (38%)	16,093 (39%)	9,139 (19%)	27,149 (57%)
Obese (>30)	11,034 (21%)	9,150 (22%)	-	20,186 (43%)
Age at menopause (years)	51 (3.9)	50 (4.1)	50 (3.9)	51 (4.1)
Early menopause (<45 years)	3,633 (6.7%)	3,569 (8.7%)	3,473 (7.3%)	3,726 (7.9%)
Late menopause (>55 years)	4,995 (9.3%)	3,471 (8.5%)	3,720 (7.9%)	4,741 (10%)
Age at menarche (years)	13 (1.6)	13 (1.6)	13 (1.5)	13 (1.6)
Lung function outcomes				
FVC%pred (%)	98 (15.6)	96.7 (15.8)	99.6 (15.3)	95.2 (15.7)
FEV_1%pred (%)	94.4 (16.2)	91.4 (17.3)	94.4 (16.6)	91.9 (16.9)
FEV_1/FVC (%)	76 (5.9)	74.4 (6.7)	74.6 (6.4)	76 (6.1)
FEV_1/FVC < LLN (N)	3,268 (6.1%)	4,705 (11.5%)	4,650 (9.8%)	3,319 (7%)
FVC < LLN (N)	3,550 (6.6%)	3,317 (8.1%)	2,471 (5.2%)	4,388 (9.3%)
Self-reported asthma (N)	6,158 (11.4%)	4,740 (11.6%)	4,738 (10.0%)	6,150 (13.0%)
Smoking status				
Never-smoker	53,831 (100%)	-	27,710 (59%)	26,080 (55%)
Ex-smoker	-	33,518 (82%)	15,777 (33%)	17,713 (37%)
Current-smoker	-	7,370 (18%)	3,826 (8%)	3534 (7%)
Pack-years in smokers	-	22 (16)	19 (14)	23 (16)
Menopausal Hormone Therapy use (MHT)				
Never used	32,705 (61%)	21,229 (52%)	27,130 (57%)	26,775 (57%)
Ex-user	18,848 (35%)	17,405 (43%)	17,520 (37%)	18,705 (40%)
Current user	2,194 (4%)	2,178 (5%)	2,612 (6%)	1761 (4%)
Oral contraceptive use ever	41,518 (77%)	34,062 (83%)	38,463 (81%)	37,076 (78%)
Townsend deprivation index	-1.99 (2.65)	-1.23 (3.04)	-1.85 (2.75)	-1.47 (2.93)
Education level				
Low (High school)	21,809 (41%)	19,781 (48%)	18,027 (38%)	23,542 (50%)
Medium (College)	9,012 (17%)	6,334 (15%)	7,796 (16%)	7,537 (16%)
High (University)	22,538 (42%)	14,359 (35%)	21,131 (45%)	15,744 (33%)
Physical activity				
Moderate	42,180 (82%)	31,334 (81%)	38,532 (85%)	34,947 (79%)
Vigorous	23,609 (46%)	17,532 (45%)	22,765 (50%)	18,361 (41%)
Live births				
0	8,886 (17%)	6,595 (16%)	8,311 (18%)	7,158 (15%)
1	6,068 (11%)	5,795 (14%)	5,891 (12%)	5,962 (13%)
2	25,837 (48%)	18,251 (45%)	22,230 (47%)	21,831 (46%)
3	9,929 (18%)	7,637 (19%)	8,450 (18%)	9,112 (19%)
>4	3,090 (6%)	2,593 (6%)	2,429 (5%)	3,250 (7%)

Table S2_A: Data for the MR analyses on menopause and lung function (SNP info).

**Height/BMI/Menarche: indicates SNPs previously associated with traits at p<7.94x10-4 (0.05/63). EA: effect allele; OA: other allele.*

								Pleiotropy*			
SNP	***CHR***	***Position (bp)***	***EA***	***OA***	***Gene***	***INFO***	***Study***	***Height***	***BMI***	***Menarche***	***Notes***
rs4246511	1	39380385	C	T	*RHBDL2*	0.961	Day, 2015				
rs12142240	1	46747301	C	T	*RAD54L*	0.999	Day, 2015				
rs1411478	1	180962282	G	A	*STX6*	1.000	Day, 2015				
rs2236918	1	242017826	G	C	*EXO1*	0.998	Day, 2015				
rs1635501	1	242040775	T	C	*EXO1*	0.988	Stolk, 2012				In LD with rs2236918 (r^2 = 0.91)
rs2303369	2	27715416	T	C	*FNDC4*	1.000	Stolk, 2012	x	x		In LD with rs704795 (r^2 = 0.98)
rs704795	2	27716494	A	G	*FNDC4*	0.999	Day, 2015	x	x		
rs1800932	2	48018081	G	A	*MSH6*	0.998	Day, 2015				
rs10496265	2	81668808	C	T	*LRRTM1*	1.000	Lunetta, 2008				F<10
rs930036	2	171941018	A	G	*TLK1*	0.999	Day, 2015	x			
rs10183486	2	171990971	T	C	*TLK1*	1.000	Stolk, 2012	x			In LD with rs930036 (r^2 = 0.87)
rs7606918	2	172895449	G	A	*METAP1D*	0.989	Stolk, 2012				F<10
rs16858210	3	183624010	A	G	*ABCC5*	0.991	Day, 2015	x			
rs4693089	4	84373622	G	A	*HELQ*	1.000	Day, 2015				
rs6856693	4	185748806	G	A	*ACSL1*	0.999	Day, 2015				
rs427394	5	6745875	G	A	*PAPD7*	0.994	Day, 2015				
rs11738223	5	171934492	G	A	*SH3PXD2B*	0.990	Day, 2015		x		
rs2241584	5	175956177	A	G	*RNF44*	0.974	Day, 2015	x			
rs890835	5	175956271	C	A	*RNF44*	1.000	Stolk, 2012				
rs691141	5	176323298	A	G	*HK3*	0.990	He, 2009	x			In LD with rs365132 (r^2 = 0.87)
rs7718874	5	176358065	G	A	*UIMC1*	0.994	He, 2009	x			In LD with rs365132 (r^2 = 1.0)
rs365132	5	176378574	T	G	*UIMC1*	1.000	Day, 2015	x		x	
rs402511	5	176434440	A	G	*UIMC1*	1.000	He, 2009	x			In LD with rs365132 (r^2 = 1.0)
rs6899676	6	10895260	G	A	*SYCP2L*	0.988	Day, 2015				
rs2153157	6	10897488	A	G	*SYCP2L*	1.000	Stolk, 2012			x	
rs9393800	6	10951737	G	A	*SYCP2L*	0.970	Day, 2015				
rs2230365	6	31525448	T	C	*NFKBIL1*	1.000	Day, 2015	x			
rs1046089	6	31602967	A	G	*PRRC2A*	1.000	Stolk, 2012				
rs707938	6	31729359	G	A	*MSH5*	1.000	Day, 2015				
rs12196873	6	111598058	C	A	*REV3L*	1.000	Day, 2015				
rs2517388	8	37977732	G	T	*ASH2L*	1.000	Stolk, 2012				In LD with rs2720044 (r^2 = 0.93)
rs2720044	8	37980587	C	A	*STAR*	0.991	Day, 2015				

								Pleiotropy*			
SNP	***CHR***	***Position (bp)***	***EA***	***OA***	***Gene***	***INFO***	***Study***	***Height***	***BMI***	***Menarche***	***Notes***
rs10957156	8	61629401	A	G	*CHD7*	0.995	Day, 2015				
rs4879656	9	33012382	A	C	*APTX*	0.997	Day, 2015				
rs10905065	10	5769827	A	G	*GDI2*	0.997	Day, 2015				
rs11031006	11	30226528	A	G	*ARL14EP*	0.993	Day, 2015	x		x	
rs6484478	11	30306440	G	A	*FSHB*	0.999	Day, 2015		x		F<10
rs12294104	11	30382899	T	C	*FSHB*	1.000	Stolk, 2012	x			
rs10734411	11	32541784	A	G	*EIF3M*	1.000	Day, 2015				
rs2277339	12	57146069	G	T	*PRIM1*	1.000	Day, 2015	x			
rs3741604	12	66696410	T	C	*HELB*	0.997	Day, 2015				
rs75770066	12	66704225	G	A	*HELB*	1.000	Day, 2015				
rs1183272	12	66735421	C	T	*GRIP1*	0.999	Day, 2015				
rs7397861	12	66814466	G	C	*HELB*	0.999	Day, 2015				
rs551087	12	121209193	A	G	*SPPL3*	0.999	Day, 2015	x			F<10
rs1727326	12	123600086	G	C	*PITPNM2*	0.985	Day, 2015	x			
rs12824058	12	130804334	G	A	*PIWIL1*	0.991	Day, 2015				
rs148126992	12	66704274			*HELB*		Day, 2015				Not available in UK biobank, but in LD with rs75770066 (r^2 = 0.73, D'= 1)
rs3736830	13	50306221	C	G	*KPNA3*	0.999	Stolk, 2012	x			
rs4886238	13	61113739	A	G	*TDRD3*	0.994	Day, 2015				
rs7333181	13	112221297	A	G	*ARHGEF7*	0.995	Stolk, 2009				F<10
rs1713460	14	20933615	G	A	*PNP*	1.000	Day, 2015				
rs9796	15	41271447	T	A	*INO80*	0.995	Day, 2015	x			
rs2307449	15	89863928	G	T	*POLG*	1.000	Stolk, 2012	x			In LD with rs1054875 (r^2 = 0.98)
rs1054875	15	89879126	T	A	*POLG*	0.991	Day, 2015	x			
rs9039	16	9205363	C	T	*C16orf72*	0.989	Day, 2015	x	x		
rs10852344	16	12016919	T	C	*GSPT1*	0.995	Day, 2015	x			
rs12599106	16	34498025	A	T	*LOC105371200*	0.999	Day, 2015				
rs8070740	17	5331896	G	A	*RPAIN*	0.998	Day, 2015		x		
rs2941505	17	37832704	G	A	*PGAP3*	0.995	Day, 2015				
rs1799949	17	41245466	A	G	*BRCA1*	1.000	Day, 2015		x		
rs349306	19	950694	A	G	*ARID3A*	0.963	Day, 2015				
rs7259376	19	22507705	G	A	*ZNF729*	0.999	Day, 2015				
rs12611091	19	55800329	C	T	*BRSK1*	1.000	He, 2009				
rs1551562	19	55814881	G	A	*BRSK1*	0.974	He, 2009				
rs1172822	19	55819845	T	C	*BRSK1*	1.000	He, 2009			x	In LD with rs11668344 (r^2 = 0.92)

								Pleiotropy*			
SNP	***CHR***	***Position (bp)***	***EA***	***OA***	***Gene***	***INFO***	***Study***	***Height***	***BMI***	***Menarche***	***Notes***
rs7246479	19	55824332	G	T	*TMEM150B*	1.000	He, 2009				In LD with rs897798 (r^2 = 0.81)
rs2384687	19	55831188	G	A	*TMEM150B*	1.000	He, 2009				In LD with rs11668344 (r^2 = 0.86)
rs11668344	19	55833664	G	A	*TMEM150B*	1.000	Day, 2015				
rs897798	19	55833754	G	A	*TMEM150B*	0.998	He, 2009				
rs2547274	19	56310228	C	G	*NLRP11*	0.970	Day, 2015				
rs12461110	19	56320663	A	G	*NLRP11*	1.000	Day, 2015				
rs236114	20	5935385	C	T	*MCM8*	1.000	Stolk, 2009				
rs451417	20	5941999	A	C	*MCM8*	0.999	Day, 2015				
rs16991615	20	5948227	A	G	*MCM8*	1.000	Day, 2015	x		x	
rs140267842	20	61288593	A	G	*SLCO4A1*	0.982	Day, 2015				
rs2236553	20	61289743	T	C	*SLCO4A1*	0.972	Day, 2015				
rs13040088	20	61549202	G	A	*DIDO1*	0.999	Day, 2015				
rs5762534	22	28633571	C	T	*CHEK2*	0.998	Day, 2015				
rs763121	22	38879940	G	A	*DDX17*	0.998	Day, 2015				

Table S2_B: Data for the MR analyses for early and late menopause (GX).

For each SNP, estimates of the gene-age at menopause associations (GX) are given in log odds ratios. EA: effect allele; EAF: effect allele frequency; F: F statistic; SE: standard errors of the related estimates. All analyses assumed an additive genetic model (per-allele genetic effect). Sample size early menopause: 86,274 and late menopause: 87,536.

			Early menopause				Late menopause			
SNP	*EA*	*EAF*	*GX*	*SE_GX*	*P_GX*	*F*	*GX*	*SE_GX*	*P_GX*	*F*
rs4246511	C	0.701	0.121	0.020	1.18E-09	**36.996**	-0.053	0.018	2.68E-03	9.015
rs12142240	C	0.306	-0.038	0.019	4.55E-02	3.998	0.125	0.017	3.36E-13	**52.985**
rs1411478	G	0.596	-0.079	0.018	7.50E-06	**20.062**	0.068	0.017	4.77E-05	**16.538**
rs2236918	G	0.548	-0.028	0.018	1.15E-01	2.478	0.067	0.016	4.21E-05	**16.776**
rs1635501	T	0.527	-0.025	0.018	1.47E-01	2.107	0.063	0.016	1.06E-04	**15.032**
rs2303369	T	0.393	0.067	0.018	1.62E-04	**14.231**	-0.099	0.017	3.60E-09	**34.828**
rs704795	A	0.397	0.070	0.018	9.06E-05	**15.323**	-0.099	0.017	3.68E-09	**34.788**
rs1800932	G	0.193	-0.092	0.023	5.21E-05	**16.368**	0.096	0.020	1.82E-06	**22.777**
rs10496265	C	0.176	-0.033	0.023	1.58E-01	1.997	0.021	0.021	3.26E-01	0.964
rs930036	A	0.381	0.079	0.018	1.03E-05	**19.462**	-0.033	0.017	4.92E-02	3.869
rs10183486	T	0.374	0.070	0.018	9.48E-05	**15.238**	-0.041	0.017	1.52E-02	5.898
rs7606918	G	0.152	0.045	0.024	5.93E-02	3.558	-0.024	0.023	2.90E-01	1.120
rs16858210	A	0.243	-0.047	0.021	2.45E-02	5.062	0.073	0.019	8.45E-05	**15.454**
rs4693089	G	0.487	-0.103	0.017	3.43E-09	**34.922**	0.158	0.016	1.42E-22	**95.574**
rs6856693	G	0.422	-0.103	0.018	6.32E-09	**33.734**	0.072	0.016	1.10E-05	**19.329**
rs427394	G	0.415	0.067	0.018	1.48E-04	**14.400**	-0.052	0.017	1.76E-03	9.781
rs11738223	G	0.333	-0.040	0.019	3.25E-02	4.570	0.032	0.017	6.41E-02	3.428
rs2241584	A	0.384	0.088	0.018	1.08E-06	**23.780**	-0.048	0.017	4.23E-03	8.181
rs890835	C	0.888	0.072	0.028	1.08E-02	6.496	-0.013	0.025	6.21E-01	0.244
rs691141	A	0.442	-0.114	0.018	1.39E-10	**41.174**	0.174	0.016	1.97E-26	**113.177**
rs7718874	G	0.477	-0.109	0.018	5.62E-10	**38.448**	0.176	0.016	2.72E-27	**117.105**
rs365132	T	0.477	-0.108	0.018	6.67E-10	**38.115**	0.173	0.016	1.85E-26	**113.309**
rs402511	A	0.477	-0.110	0.018	3.78E-10	**39.222**	0.175	0.016	5.91E-27	**115.568**
rs6899676	G	0.199	-0.097	0.023	1.73E-05	**18.469**	0.135	0.020	5.78E-12	**47.404**
rs2153157	A	0.493	-0.055	0.017	1.50E-03	**10.079**	0.096	0.016	2.70E-09	**35.386**
rs9393800	G	0.274	0.090	0.019	3.50E-06	**21.519**	-0.114	0.019	1.65E-09	**36.350**
rs2230365	T	0.141	-0.077	0.026	2.72E-03	8.985	0.056	0.023	1.37E-02	6.075
rs1046089	A	0.361	0.092	0.018	3.49E-07	**25.956**	-0.089	0.017	1.71E-07	**27.335**
rs707938	G	0.324	0.066	0.018	3.43E-04	**12.818**	-0.074	0.018	2.50E-05	**17.763**
rs12196873	C	0.144	-0.027	0.025	2.74E-01	1.195	0.087	0.022	1.06E-04	**15.035**
rs2517388	G	0.173	-0.120	0.024	4.84E-07	**25.326**	0.106	0.021	3.56E-07	**25.920**
rs2720044	C	0.163	-0.129	0.025	1.76E-07	**27.275**	0.113	0.021	1.28E-07	**27.891**
rs10957156	A	0.753	0.062	0.021	2.38E-03	9.227	-0.031	0.019	9.58E-02	2.774
rs4879656	A	0.378	0.054	0.018	2.36E-03	9.249	-0.039	0.017	1.93E-02	5.475
rs10905065	A	0.606	0.024	0.018	1.73E-01	1.856	-0.059	0.017	3.47E-04	**12.799**
rs11031006	A	0.145	-0.061	0.025	1.61E-02	5.791	0.066	0.023	3.55E-03	8.499
rs6484478	G	0.772	-0.032	0.021	1.19E-01	2.436	0.005	0.019	7.96E-01	0.067
rs12294104	T	0.176	-0.047	0.023	4.55E-02	4.000	0.034	0.021	1.07E-01	2.605
rs10734411	A	0.482	0.060	0.017	6.29E-04	**11.689**	-0.023	0.016	1.53E-01	2.045
rs2277339	G	0.106	0.145	0.027	7.19E-08	**29.012**	-0.217	0.029	2.91E-14	**57.796**
rs3741604	T	0.528	0.054	0.018	2.26E-03	9.323	-0.080	0.016	8.87E-07	**24.159**
rs75770066	G	0.030	-0.390	0.061	2.02E-10	**40.443**	0.529	0.039	1.08E-42	**187.572**
rs1183272	C	0.446	0.021	0.018	2.26E-01	1.465	-0.031	0.016	5.37E-02	3.721
rs7397861	G	0.633	0.009	0.018	6.20E-01	0.245	-0.068	0.017	4.46E-05	**16.666**
rs551087	A	0.714	0.054	0.019	5.25E-03	7.791	0.039	0.018	3.13E-02	4.638
rs1727326	G	0.860	-0.073	0.025	3.06E-03	8.774	0.069	0.024	3.77E-03	8.389

			Early menopause				Late menopause			
SNP	***EA***	***EAF***	***GX***	***SE_GX***	***P_GX***	***F***	***GX***	***SE_GX***	***P_GX***	***F***
rs12824058	G	0.419	0.046	0.018	8.50E-03	6.925	-0.053	0.017	1.45E-03	**10.138**
rs3736830	C	0.852	-0.011	0.024	6.59E-01	0.195	0.110	0.024	2.91E-06	**21.874**
rs4886238	A	0.327	-0.097	0.019	3.35E-07	**26.036**	0.047	0.017	5.92E-03	7.576
rs7333181	A	0.135	-0.063	0.026	1.63E-02	5.772	-0.022	0.024	3.50E-01	0.875
rs1713460	G	0.313	0.040	0.019	3.03E-02	4.691	-0.075	0.018	2.13E-05	**18.073**
rs9796	T	0.473	0.067	0.018	1.34E-04	**14.586**	-0.087	0.016	9.84E-08	**28.405**
rs2307449	G	0.391	0.047	0.018	8.64E-03	6.895	-0.087	0.017	1.92E-07	**27.116**
rs1054875	T	0.393	0.046	0.018	9.51E-03	6.724	-0.090	0.017	8.15E-08	**28.771**
rs9039	C	0.271	0.068	0.019	4.59E-04	**12.276**	-0.015	0.018	4.14E-01	0.667
rs10852344	T	0.596	0.103	0.018	1.04E-08	**32.768**	-0.100	0.016	1.17E-09	**37.015**
rs12599106	A	0.503	0.064	0.018	2.37E-04	**13.514**	-0.039	0.016	1.68E-02	5.722
rs8070740	G	0.242	-0.046	0.021	2.63E-02	4.934	0.083	0.019	7.82E-06	**19.982**
rs2941505	G	0.685	-0.068	0.019	2.56E-04	**13.367**	0.058	0.018	9.54E-04	**10.914**
rs1799949	A	0.324	-0.076	0.019	6.00E-05	**16.102**	0.082	0.017	1.37E-06	**23.316**
rs349306	A	0.872	-0.124	0.026	1.23E-06	**23.533**	0.080	0.026	1.79E-03	9.752
rs7259376	G	0.535	-0.050	0.017	4.48E-03	8.076	0.030	0.016	6.09E-02	3.512
rs12611091	C	0.490	-0.189	0.017	3.36E-27	**116.686**	0.075	0.016	3.63E-06	**21.453**
rs1551562	G	0.234	0.209	0.020	1.86E-25	**108.725**	-0.088	0.020	1.02E-05	**19.477**
rs1172822	T	0.376	0.245	0.018	1.11E-43	**192.088**	-0.113	0.017	2.61E-11	**44.446**
rs7246479	G	0.514	0.215	0.018	3.32E-34	**148.708**	-0.086	0.016	1.08E-07	**28.227**
rs2384687	G	0.398	0.225	0.018	1.96E-37	**163.489**	-0.131	0.017	8.55E-15	**60.204**
rs11668344	G	0.364	0.254	0.018	1.80E-46	**204.880**	-0.136	0.017	2.85E-15	**62.364**
rs897798	G	0.466	0.241	0.017	3.13E-43	**190.032**	-0.097	0.016	3.12E-09	**35.108**
rs2547274	C	0.093	-0.122	0.032	1.28E-04	**14.677**	0.052	0.028	6.17E-02	3.492
rs12461110	A	0.365	0.075	0.018	3.39E-05	**17.187**	-0.029	0.017	8.36E-02	2.993
rs236114	C	0.796	0.078	0.022	4.47E-04	**12.324**	-0.169	0.019	2.29E-18	**76.420**
rs451417	A	0.124	0.119	0.025	2.84E-06	**21.922**	-0.119	0.026	3.76E-06	**21.382**
rs16991615	A	0.062	-0.387	0.043	2.66E-19	**80.678**	0.514	0.028	3.39E-74	**332.079**
rs140267842	A	0.009	-0.269	0.103	8.83E-03	6.857	0.195	0.078	1.27E-02	6.216
rs2236553	T	0.753	-0.108	0.020	5.70E-08	**29.464**	0.076	0.019	9.02E-05	**15.332**
rs13040088	G	0.213	0.094	0.021	6.21E-06	**20.423**	-0.077	0.020	1.39E-04	**14.513**
rs5762534	C	0.147	-0.062	0.025	1.37E-02	6.075	0.035	0.023	1.23E-01	2.374
rs763121	G	0.343	0.105	0.018	6.14E-09	**33.788**	-0.060	0.017	4.64E-04	**12.254**

Table S2_C: Data for the MR analyses on FEV_1/FVC and FEV_1/FVC < LLN (GY).

For each SNP, estimates of the gene-Lung function outcomes (GY) are given for FEV_1/FVC and FEV_1/FVC < LLN. EA: effect allele; EAF: effect allele frequency; SE: standard errors of the related estimates; All analyses assumed an additive genetic model (per-allele genetic effect). Effect estimates represent log odds ratios for FEV_1/FVC < LLN and % change for FEV_1/FVC. Sample size early menopause: 86,274 and late menopause: 87,536.

			Early menopause						Late menopause					
			FEV_1/FVC			FEV_1/FVC < LLN			FEV_1/FVC			FEV_1/FVC < LLN		
SNP	*EA*	*EAF*	*GY*	*SE_GY*	*P_GY*	*GY*	*SE_GY*	*P_GY*	*GY*	*SE_GY*	*P_GY*	*GY*	*SE_GY*	*P_GY*
rs4246511	C	0.701	0.028	0.033	3.96E-01	-0.021	0.019	2.89E-01	0.031	0.032	3.41E-01	-0.008	0.019	6.73E-01
rs12142240	C	0.306	-0.050	0.032	1.18E-01	0.030	0.019	1.19E-01	-0.039	0.032	2.16E-01	0.015	0.019	4.37E-01
rs1411478	G	0.596	-0.127	0.030	2.27E-05	0.024	0.018	1.85E-01	-0.134	0.030	7.19E-06	0.033	0.018	6.76E-02
rs2236918	G	0.548	0.046	0.030	1.19E-01	-0.009	0.018	5.89E-01	0.026	0.029	3.75E-01	-0.001	0.018	9.51E-01
rs1635501	T	0.527	0.036	0.030	2.20E-01	-0.003	0.018	8.87E-01	0.017	0.029	5.61E-01	0.003	0.018	8.49E-01
rs2303369	T	0.393	-0.014	0.030	6.41E-01	0.009	0.018	6.26E-01	-0.004	0.030	9.00E-01	0.012	0.018	5.17E-01
rs704795	A	0.397	-0.007	0.030	8.07E-01	0.004	0.018	8.24E-01	0.001	0.030	9.60E-01	0.009	0.018	6.31E-01
rs1800932	G	0.193	0.088	0.037	1.82E-02	-0.029	0.022	1.90E-01	0.070	0.037	5.76E-02	-0.021	0.022	3.43E-01
rs10496265	C	0.176	0.039	0.039	3.17E-01	-0.017	0.023	4.61E-01	0.029	0.038	4.53E-01	-0.015	0.023	5.10E-01
rs930036	A	0.381	0.016	0.030	6.03E-01	-0.012	0.018	5.17E-01	0.022	0.030	4.72E-01	-0.018	0.018	3.09E-01
rs10183486	T	0.374	0.016	0.030	6.01E-01	-0.013	0.018	4.70E-01	0.029	0.030	3.34E-01	-0.022	0.018	2.20E-01
rs7606918	G	0.152	0.053	0.041	1.99E-01	-0.022	0.025	3.73E-01	0.027	0.041	5.08E-01	-0.027	0.025	2.71E-01
rs16858210	A	0.243	-0.006	0.035	8.58E-01	0.005	0.021	8.11E-01	-0.022	0.034	5.25E-01	0.016	0.021	4.37E-01
rs4693089	G	0.487	-0.015	0.029	6.03E-01	0.024	0.017	1.76E-01	-0.048	0.029	9.83E-02	0.025	0.018	1.61E-01
rs6856693	G	0.422	-0.077	0.030	9.46E-03	0.019	0.018	2.93E-01	-0.079	0.029	7.37E-03	0.020	0.018	2.63E-01
rs427394	G	0.415	0.054	0.030	7.13E-02	-0.028	0.018	1.14E-01	0.035	0.030	2.31E-01	-0.018	0.018	3.23E-01
rs11738223	G	0.333	0.008	0.031	7.92E-01	0.000	0.019	9.96E-01	0.024	0.031	4.40E-01	0.001	0.019	9.52E-01
rs2241584	A	0.384	0.001	0.031	9.81E-01	0.004	0.018	8.19E-01	-0.024	0.030	4.23E-01	0.017	0.018	3.53E-01
rs890835	C	0.888	-0.009	0.047	8.55E-01	0.009	0.028	7.45E-01	-0.037	0.046	4.28E-01	0.017	0.028	5.44E-01
rs691141	A	0.442	-0.006	0.030	8.39E-01	-0.008	0.018	6.39E-01	-0.006	0.029	8.33E-01	-0.012	0.018	4.90E-01
rs7718874	G	0.477	-0.011	0.030	7.16E-01	-0.005	0.018	7.75E-01	-0.009	0.029	7.64E-01	-0.008	0.018	6.39E-01
rs365132	T	0.477	-0.007	0.030	8.08E-01	-0.006	0.018	7.16E-01	-0.007	0.029	8.11E-01	-0.009	0.018	6.12E-01
rs402511	A	0.477	-0.007	0.030	8.01E-01	-0.006	0.018	7.28E-01	-0.006	0.029	8.34E-01	-0.009	0.018	6.09E-01
rs6899676	G	0.199	0.003	0.037	9.36E-01	-0.017	0.022	4.36E-01	0.006	0.036	8.74E-01	-0.019	0.022	3.92E-01
rs2153157	A	0.493	0.043	0.029	1.48E-01	-0.006	0.017	7.39E-01	0.022	0.029	4.54E-01	0.001	0.018	9.59E-01
rs9393800	G	0.274	0.015	0.033	6.53E-01	-0.012	0.020	5.49E-01	-0.003	0.033	9.35E-01	-0.005	0.020	7.86E-01
rs2230365	T	0.141	-0.007	0.042	8.69E-01	0.001	0.025	9.81E-01	-0.027	0.042	5.14E-01	0.012	0.025	6.24E-01
rs1046089	A	0.361	-0.145	0.031	2.32E-06	0.046	0.018	1.11E-02	-0.147	0.030	1.44E-06	0.046	0.018	1.19E-02
rs707938	G	0.324	-0.098	0.031	1.77E-03	0.013	0.019	4.87E-01	-0.105	0.031	7.72E-04	0.009	0.019	6.20E-01

			Early menopause						Late menopause					
			FEV_1/FVC			FEV_1/FVC < LLN			FEV_1/FVC			FEV_1/FVC < LLN		
SNP	*EA*	*EAF*	*GY*	*SE_GY*	*P_GY*	*GY*	*SE_GY*	*P_GY*	*GY*	*SE_GY*	*P_GY*	*GY*	*SE_GY*	*P_GY*
rs12196873	C	0.144	-0.025	0.042	5.54E-01	0.016	0.025	5.28E-01	-0.033	0.041	4.22E-01	0.025	0.025	3.12E-01
rs2517388	G	0.173	0.018	0.039	6.45E-01	0.011	0.023	6.23E-01	0.010	0.038	7.88E-01	0.018	0.023	4.33E-01
rs2720044	C	0.163	0.012	0.040	7.63E-01	0.007	0.024	7.69E-01	0.009	0.039	8.20E-01	0.013	0.024	5.80E-01
rs10957156	A	0.753	0.000	0.034	9.96E-01	-0.006	0.020	7.54E-01	-0.006	0.034	8.49E-01	-0.008	0.020	7.11E-01
rs4879656	A	0.378	0.050	0.030	9.66E-02	-0.014	0.018	4.37E-01	0.042	0.030	1.63E-01	-0.012	0.018	4.96E-01
rs10905065	A	0.606	0.007	0.030	8.25E-01	-0.008	0.018	6.41E-01	0.009	0.030	7.55E-01	-0.015	0.018	4.07E-01
rs11031006	A	0.145	-0.093	0.042	2.64E-02	0.034	0.025	1.65E-01	-0.097	0.041	1.90E-02	0.043	0.025	8.42E-02
rs6484478	G	0.772	-0.043	0.035	2.20E-01	0.040	0.021	5.89E-02	-0.031	0.035	3.70E-01	0.031	0.021	1.41E-01
rs12294104	T	0.176	-0.076	0.039	5.07E-02	0.028	0.023	2.25E-01	-0.075	0.038	5.03E-02	0.031	0.023	1.75E-01
rs10734411	A	0.482	0.070	0.029	1.78E-02	-0.020	0.017	2.62E-01	0.075	0.029	1.04E-02	-0.024	0.018	1.70E-01
rs2277339	G	0.106	0.095	0.048	4.69E-02	-0.023	0.028	4.21E-01	0.077	0.048	1.08E-01	-0.023	0.029	4.24E-01
rs3741604	T	0.528	-0.013	0.030	6.61E-01	0.006	0.018	7.22E-01	-0.004	0.029	8.82E-01	-0.005	0.018	7.87E-01
rs75770066	G	0.030	0.001	0.088	9.90E-01	-0.055	0.053	2.98E-01	0.010	0.084	9.04E-01	-0.071	0.052	1.70E-01
rs1183272	C	0.446	0.034	0.030	2.53E-01	-0.007	0.018	6.76E-01	0.035	0.029	2.38E-01	-0.007	0.018	6.75E-01
rs7397861	G	0.633	0.004	0.031	8.91E-01	0.007	0.018	7.04E-01	-0.010	0.030	7.35E-01	0.020	0.018	2.75E-01
rs551087	A	0.714	0.046	0.033	1.58E-01	-0.031	0.019	1.10E-01	0.055	0.032	8.59E-02	-0.031	0.019	1.07E-01
rs1727326	G	0.860	0.037	0.042	3.79E-01	-0.003	0.025	9.00E-01	0.042	0.042	3.14E-01	-0.006	0.025	8.21E-01
rs12824058	G	0.419	0.015	0.030	6.23E-01	0.008	0.018	6.39E-01	0.033	0.030	2.65E-01	0.005	0.018	7.71E-01
rs3736830	C	0.852	0.052	0.041	2.04E-01	-0.019	0.024	4.46E-01	0.053	0.041	1.99E-01	-0.018	0.025	4.61E-01
rs4886238	A	0.327	-0.021	0.032	5.08E-01	0.009	0.019	6.29E-01	-0.045	0.031	1.49E-01	0.015	0.019	4.14E-01
rs7333181	A	0.135	-0.008	0.043	8.53E-01	0.005	0.026	8.51E-01	-0.053	0.043	2.16E-01	0.031	0.026	2.24E-01
rs1713460	G	0.313	-0.037	0.032	2.44E-01	0.014	0.019	4.67E-01	-0.037	0.031	2.36E-01	0.010	0.019	6.10E-01
rs9796	T	0.473	-0.020	0.030	4.94E-01	0.005	0.018	7.83E-01	-0.016	0.029	5.78E-01	0.005	0.018	7.98E-01
rs2307449	G	0.391	0.028	0.030	3.51E-01	-0.033	0.018	6.66E-02	0.036	0.030	2.27E-01	-0.031	0.018	8.45E-02
rs1054875	T	0.393	0.030	0.030	3.21E-01	-0.037	0.018	4.11E-02	0.036	0.030	2.29E-01	-0.033	0.018	6.75E-02
rs9039	C	0.271	0.057	0.033	8.47E-02	-0.033	0.020	1.02E-01	0.025	0.033	4.50E-01	-0.023	0.020	2.45E-01
rs10852344	T	0.596	0.046	0.030	1.22E-01	-0.036	0.018	4.12E-02	0.055	0.030	6.56E-02	-0.045	0.018	1.15E-02
rs12599106	A	0.503	-0.011	0.030	7.16E-01	0.025	0.018	1.53E-01	0.008	0.029	7.94E-01	0.024	0.018	1.81E-01
rs8070740	G	0.242	-0.103	0.034	2.92E-03	0.042	0.020	3.93E-02	-0.102	0.034	2.63E-03	0.046	0.020	2.42E-02
rs2941505	G	0.685	0.007	0.032	8.13E-01	-0.023	0.019	2.14E-01	0.025	0.031	4.31E-01	-0.032	0.019	8.76E-02
rs1799949	A	0.324	-0.002	0.031	9.58E-01	0.001	0.019	9.43E-01	-0.007	0.031	8.12E-01	0.009	0.019	6.39E-01
rs349306	A	0.872	-0.030	0.045	4.99E-01	-0.013	0.026	6.15E-01	-0.023	0.045	6.03E-01	-0.018	0.027	5.12E-01
rs7259376	G	0.535	0.004	0.030	8.82E-01	0.001	0.018	9.60E-01	0.014	0.029	6.21E-01	-0.003	0.018	8.80E-01
rs12611091	C	0.490	-0.059	0.029	4.33E-02	0.049	0.017	5.35E-03	-0.047	0.029	1.08E-01	0.032	0.018	7.05E-02

			Early menopause						Late menopause					
			FEV$_1$/FVC			*FEV$_1$/FVC < LLN*			*FEV$_1$/FVC*			*FEV$_1$/FVC < LLN*		
SNP	***EA***	***EAF***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***
rs1551562	G	0.234	0.080	0.035	2.24E-02	-0.031	0.021	1.41E-01	0.054	0.035	1.26E-01	-0.019	0.021	3.58E-01
rs1172822	T	0.376	0.097	0.030	1.38E-03	-0.046	0.018	1.16E-02	0.089	0.030	3.35E-03	-0.037	0.018	4.00E-02
rs7246479	G	0.514	0.079	0.029	7.35E-03	-0.032	0.017	6.88E-02	0.078	0.029	7.39E-03	-0.024	0.018	1.76E-01
rs2384687	G	0.398	0.121	0.030	5.39E-05	-0.042	0.018	1.80E-02	0.113	0.030	1.58E-04	-0.033	0.018	6.46E-02
rs11668344	G	0.364	0.115	0.031	1.54E-04	-0.052	0.018	4.10E-03	0.106	0.030	4.64E-04	-0.042	0.018	2.15E-02
rs897798	G	0.466	0.085	0.029	3.88E-03	-0.046	0.018	8.53E-03	0.080	0.029	6.34E-03	-0.036	0.018	4.09E-02
rs2547274	C	0.093	-0.048	0.051	3.49E-01	0.033	0.030	2.77E-01	-0.022	0.051	6.69E-01	0.020	0.030	5.15E-01
rs12461110	A	0.365	0.026	0.031	4.02E-01	-0.051	0.018	5.48E-03	0.020	0.030	5.20E-01	-0.051	0.018	5.57E-03
rs236114	C	0.796	0.041	0.037	2.69E-01	-0.003	0.022	8.83E-01	-0.006	0.036	8.76E-01	0.024	0.022	2.80E-01
rs451417	A	0.124	0.127	0.045	4.20E-03	-0.053	0.027	5.06E-02	0.073	0.044	1.02E-01	-0.016	0.027	5.42E-01
rs16991615	A	0.062	-0.146	0.063	1.93E-02	0.036	0.037	3.29E-01	-0.084	0.060	1.61E-01	0.007	0.036	8.36E-01
rs140267842	A	0.009	-0.080	0.155	6.05E-01	-0.123	0.097	2.06E-01	-0.136	0.151	3.69E-01	-0.053	0.093	5.71E-01
rs2236553	T	0.753	-0.083	0.034	1.64E-02	0.026	0.021	2.00E-01	-0.057	0.034	9.74E-02	0.022	0.021	2.95E-01
rs13040088	G	0.213	-0.040	0.036	2.65E-01	0.009	0.021	6.76E-01	-0.037	0.036	3.04E-01	0.004	0.022	8.44E-01
rs5762534	C	0.147	-0.037	0.041	3.71E-01	-0.008	0.025	7.37E-01	-0.044	0.041	2.78E-01	0.009	0.025	7.15E-01
rs763121	G	0.343	-0.015	0.031	6.29E-01	-0.001	0.018	9.75E-01	-0.034	0.031	2.67E-01	0.006	0.019	7.45E-01

Table S2_D: Data for the MR analyses on FVC and FVC < LLN (GY).

For each SNP, estimates of the gene-Lung function outcomes (GY) are given for FVC and FVC < LLN. EA: effect allele; EAF: effect allele frequency; SE: standard errors of the related estimates; All analyses assumed an additive genetic model (per-allele genetic effect). Effect estimates represent log odds ratios for FVC < LLN and mL change for FVC. Sample size early menopause: 86,274 and late menopause: 87,536.

			Early menopause						**Late menopause**					
			FVC			***FVC < LLN***			***FVC***			***FVC < LLN***		
SNP	***EA***	***EAF***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***
rs4246511	C	0.701	0.377	2.608	8.85E-01	-0.013	0.021	5.46E-01	1.373	2.565	5.92E-01	-0.031	0.021	1.39E-01
rs12142240	C	0.306	-2.876	2.543	2.58E-01	0.004	0.021	8.42E-01	-4.529	2.501	7.01E-02	0.012	0.021	5.58E-01
rs1411478	G	0.596	-0.037	2.389	9.88E-01	0.026	0.020	1.77E-01	-1.340	2.361	5.70E-01	0.033	0.020	9.56E-02
rs2236918	G	0.548	-2.617	2.354	2.66E-01	0.046	0.019	1.74E-02	-3.301	2.325	1.56E-01	0.055	0.019	4.63E-03
rs1635501	T	0.527	-3.136	2.356	1.83E-01	0.048	0.019	1.25E-02	-3.301	2.326	1.56E-01	0.055	0.019	4.61E-03
rs2303369	T	0.393	-0.795	2.401	7.40E-01	0.001	0.020	9.49E-01	-0.649	2.372	7.84E-01	-0.001	0.020	9.71E-01
rs704795	A	0.397	-0.083	2.398	9.73E-01	0.002	0.020	9.13E-01	0.003	2.369	9.99E-01	-0.001	0.020	9.60E-01
rs1800932	G	0.193	-9.187	2.975	2.02E-03	0.036	0.024	1.34E-01	-8.755	2.926	2.77E-03	0.034	0.024	1.63E-01
rs10496265	C	0.176	2.631	3.083	3.93E-01	-0.023	0.025	3.71E-01	4.471	3.038	1.41E-01	-0.048	0.026	6.08E-02
rs930036	A	0.381	-4.297	2.406	7.41E-02	0.008	0.020	6.74E-01	-4.504	2.378	5.83E-02	-0.007	0.020	7.05E-01
rs10183486	T	0.374	-5.221	2.413	3.05E-02	0.010	0.020	6.16E-01	-6.297	2.385	8.29E-03	0.001	0.020	9.74E-01
rs7606918	G	0.152	2.129	3.270	5.15E-01	-0.005	0.027	8.40E-01	3.995	3.237	2.17E-01	-0.026	0.027	3.27E-01
rs16858210	A	0.243	-7.943	2.747	3.84E-03	0.006	0.022	7.90E-01	-8.841	2.705	1.08E-03	0.011	0.022	6.37E-01
rs4693089	G	0.487	-1.039	2.336	6.57E-01	-0.007	0.019	7.10E-01	-2.192	2.307	3.42E-01	0.000	0.019	9.83E-01
rs6856693	G	0.422	-2.454	2.366	3.00E-01	-0.012	0.019	5.24E-01	-2.088	2.334	3.71E-01	-0.016	0.019	4.13E-01
rs427394	G	0.415	1.058	2.374	6.56E-01	-0.020	0.019	2.95E-01	1.180	2.348	6.15E-01	-0.018	0.020	3.43E-01
rs11738223	G	0.333	0.334	2.492	8.93E-01	0.030	0.020	1.37E-01	-1.220	2.457	6.19E-01	0.039	0.020	5.66E-02
rs2241584	A	0.384	-2.500	2.432	3.04E-01	-0.012	0.020	5.47E-01	-0.891	2.403	7.11E-01	-0.013	0.020	5.11E-01
rs890835	C	0.888	1.776	3.711	6.32E-01	-0.008	0.030	7.91E-01	2.558	3.653	4.84E-01	0.001	0.030	9.77E-01
rs691141	A	0.442	-1.855	2.374	4.35E-01	-0.012	0.019	5.30E-01	-2.440	2.338	2.97E-01	-0.004	0.019	8.27E-01
rs7718874	G	0.477	-1.738	2.355	4.61E-01	-0.003	0.019	8.59E-01	-1.883	2.322	4.17E-01	-0.001	0.019	9.63E-01
rs365132	T	0.477	-1.534	2.349	5.14E-01	-0.005	0.019	8.09E-01	-1.687	2.317	4.66E-01	-0.002	0.019	9.33E-01
rs402511	A	0.477	-1.757	2.348	4.54E-01	-0.004	0.019	8.53E-01	-1.851	2.316	4.24E-01	-0.001	0.019	9.57E-01
rs6899676	G	0.199	-1.520	2.953	6.07E-01	0.012	0.024	6.18E-01	-3.694	2.894	2.02E-01	0.023	0.024	3.30E-01
rs2153157	A	0.493	-2.251	2.339	3.36E-01	0.002	0.019	9.21E-01	-2.038	2.307	3.77E-01	0.002	0.019	8.98E-01
rs9393800	G	0.274	0.581	2.650	8.26E-01	0.009	0.022	6.62E-01	0.921	2.628	7.26E-01	0.014	0.022	5.33E-01
rs2230365	T	0.141	5.078	3.354	1.30E-01	-0.007	0.028	7.91E-01	5.219	3.297	1.13E-01	-0.010	0.028	7.25E-01
rs1046089	A	0.361	-4.366	2.437	7.32E-02	0.026	0.020	1.87E-01	-5.682	2.413	1.85E-02	0.034	0.020	8.45E-02
rs707938	G	0.324	-2.555	2.502	3.07E-01	0.018	0.020	3.83E-01	-4.600	2.475	6.31E-02	0.028	0.020	1.72E-01

			Early menopause						Late menopause					
			FVC			*FVC < LLN*			*FVC*			*FVC < LLN*		
SNP	***EA***	***EAF***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***
rs12196873	C	0.144	0.517	3.336	8.77E-01	-0.008	0.027	7.77E-01	1.178	3.284	7.20E-01	0.005	0.027	8.58E-01
rs2517388	G	0.173	0.685	3.102	8.25E-01	0.029	0.025	2.47E-01	1.790	3.045	5.57E-01	0.024	0.025	3.39E-01
rs2720044	C	0.163	0.451	3.194	8.88E-01	0.026	0.026	3.16E-01	1.869	3.132	5.51E-01	0.018	0.026	4.87E-01
rs10957156	A	0.753	-1.344	2.723	6.22E-01	0.026	0.022	2.49E-01	-1.048	2.682	6.96E-01	0.027	0.022	2.27E-01
rs4879656	A	0.378	0.107	2.403	9.65E-01	0.002	0.020	9.38E-01	-0.249	2.379	9.17E-01	0.013	0.020	5.15E-01
rs10905065	A	0.606	-0.561	2.400	8.15E-01	-0.037	0.020	6.16E-02	0.322	2.368	8.92E-01	-0.035	0.020	7.09E-02
rs11031006	A	0.145	0.731	3.341	8.27E-01	0.027	0.027	3.26E-01	1.436	3.285	6.62E-01	0.020	0.027	4.60E-01
rs6484478	G	0.772	-3.841	2.788	1.68E-01	0.016	0.023	4.74E-01	-1.544	2.754	5.75E-01	0.015	0.023	5.25E-01
rs12294104	T	0.176	-0.400	3.085	8.97E-01	0.025	0.025	3.27E-01	0.521	3.036	8.64E-01	0.015	0.025	5.41E-01
rs10734411	A	0.482	1.390	2.338	5.52E-01	0.012	0.019	5.41E-01	2.555	2.312	2.69E-01	-0.002	0.019	8.98E-01
rs2277339	G	0.106	5.592	3.786	1.40E-01	0.002	0.031	9.58E-01	7.661	3.790	4.32E-02	-0.006	0.031	8.41E-01
rs3741604	T	0.528	-2.448	2.356	2.99E-01	0.012	0.019	5.39E-01	-2.300	2.323	3.22E-01	0.004	0.019	8.52E-01
rs75770066	G	0.030	-12.678	6.982	6.94E-02	0.090	0.055	1.01E-01	-8.375	6.631	2.07E-01	0.085	0.054	1.13E-01
rs1183272	C	0.446	6.291	2.355	7.56E-03	-0.019	0.019	3.29E-01	6.577	2.324	4.66E-03	-0.019	0.019	3.29E-01
rs7397861	G	0.633	-1.890	2.434	4.37E-01	0.000	0.020	9.97E-01	-0.981	2.399	6.83E-01	-0.005	0.020	7.96E-01
rs551087	A	0.714	7.590	2.586	3.34E-03	-0.036	0.021	8.48E-02	8.523	2.553	8.45E-04	-0.040	0.021	5.71E-02
rs1727326	G	0.860	8.236	3.368	1.45E-02	-0.056	0.027	3.96E-02	7.710	3.340	2.10E-02	-0.034	0.028	2.16E-01
rs12824058	G	0.419	3.941	2.377	9.73E-02	-0.032	0.019	1.00E-01	3.340	2.353	1.56E-01	-0.031	0.020	1.13E-01
rs3736830	C	0.852	-1.677	3.282	6.09E-01	0.013	0.027	6.23E-01	-1.364	3.248	6.75E-01	0.008	0.027	7.67E-01
rs4886238	A	0.327	7.223	2.510	4.00E-03	-0.003	0.020	8.88E-01	6.875	2.472	5.41E-03	-0.007	0.021	7.35E-01
rs7333181	A	0.135	-1.555	3.432	6.50E-01	0.051	0.028	6.87E-02	-3.559	3.383	2.93E-01	0.067	0.028	1.53E-02
rs1713460	G	0.313	3.167	2.512	2.07E-01	0.005	0.020	8.20E-01	3.858	2.484	1.20E-01	0.015	0.021	4.66E-01
rs9796	T	0.473	9.112	2.351	1.07E-04	-0.041	0.019	3.26E-02	8.759	2.321	1.61E-04	-0.041	0.019	3.47E-02
rs2307449	G	0.391	4.212	2.393	7.84E-02	-0.016	0.020	4.02E-01	4.886	2.366	3.89E-02	-0.036	0.020	6.78E-02
rs1054875	T	0.393	4.744	2.401	4.81E-02	-0.020	0.020	3.15E-01	5.415	2.373	2.25E-02	-0.040	0.020	4.16E-02
rs9039	C	0.271	-5.586	2.648	3.49E-02	0.017	0.022	4.37E-01	-5.345	2.617	4.11E-02	0.016	0.022	4.59E-01
rs10852344	T	0.596	-1.392	2.387	5.60E-01	0.003	0.020	8.71E-01	-0.283	2.357	9.04E-01	-0.009	0.020	6.37E-01
rs12599106	A	0.503	1.085	2.351	6.44E-01	-0.005	0.019	8.11E-01	1.292	2.324	5.78E-01	-0.024	0.019	2.16E-01
rs8070740	G	0.242	-0.422	2.743	8.78E-01	0.035	0.022	1.16E-01	1.238	2.702	6.47E-01	0.031	0.022	1.70E-01
rs2941505	G	0.685	3.001	2.517	2.33E-01	0.013	0.021	5.38E-01	3.110	2.486	2.11E-01	0.004	0.021	8.54E-01
rs1799949	A	0.324	5.629	2.502	2.45E-02	-0.055	0.021	7.73E-03	5.464	2.462	2.65E-02	-0.049	0.021	1.64E-02
rs349306	A	0.872	4.833	3.568	1.75E-01	-0.023	0.029	4.29E-01	2.630	3.546	4.58E-01	-0.005	0.029	8.78E-01
rs7259376	G	0.535	2.690	2.349	2.52E-01	0.004	0.019	8.36E-01	2.495	2.318	2.82E-01	0.002	0.019	9.02E-01
rs12611091	C	0.490	3.393	2.334	1.46E-01	-0.021	0.019	2.73E-01	4.148	2.310	7.25E-02	-0.026	0.019	1.74E-01

			Early menopause						Late menopause					
			FVC			***FVC < LLN***			***FVC***			***FVC < LLN***		
SNP	***EA***	***EAF***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***
rs1551562	G	0.234	-5.851	2.796	3.64E-02	0.043	0.023	5.44E-02	-6.099	2.782	2.84E-02	0.044	0.023	5.23E-02
rs1172822	T	0.376	-3.547	2.414	1.42E-01	0.014	0.020	4.91E-01	-3.601	2.394	1.33E-01	0.009	0.020	6.37E-01
rs7246479	G	0.514	-3.981	2.343	8.93E-02	0.018	0.019	3.33E-01	-4.098	2.316	7.69E-02	0.017	0.019	3.63E-01
rs2384687	G	0.398	-4.393	2.393	6.63E-02	0.017	0.019	3.91E-01	-4.599	2.371	5.25E-02	0.009	0.020	6.57E-01
rs11668344	G	0.364	-2.937	2.427	2.26E-01	0.015	0.020	4.53E-01	-3.221	2.410	1.81E-01	0.006	0.020	7.59E-01
rs897798	G	0.466	-2.527	2.340	2.80E-01	0.014	0.019	4.56E-01	-2.586	2.320	2.65E-01	0.008	0.019	6.61E-01
rs2547274	C	0.093	-7.992	4.091	5.08E-02	0.082	0.033	1.18E-02	-6.368	4.018	1.13E-01	0.069	0.033	3.57E-02
rs12461110	A	0.365	4.397	2.435	7.10E-02	-0.023	0.020	2.41E-01	3.939	2.406	1.02E-01	-0.013	0.020	5.16E-01
rs236114	C	0.796	3.776	2.913	1.95E-01	0.000	0.024	9.99E-01	3.042	2.856	2.87E-01	0.011	0.024	6.32E-01
rs451417	A	0.124	9.687	3.541	6.23E-03	-0.032	0.029	2.79E-01	7.338	3.525	3.74E-02	-0.020	0.029	4.97E-01
rs16991615	A	0.062	-0.503	4.975	9.19E-01	-0.034	0.041	4.05E-01	-1.750	4.728	7.11E-01	-0.048	0.040	2.34E-01
rs140267842	A	0.009	18.861	12.364	1.27E-01	-0.169	0.108	1.15E-01	16.639	11.974	1.65E-01	-0.185	0.107	8.27E-02
rs2236553	T	0.753	1.270	2.742	6.43E-01	0.000	0.022	9.84E-01	2.105	2.719	4.39E-01	-0.013	0.023	5.75E-01
rs13040088	G	0.213	4.439	2.851	1.19E-01	-0.033	0.024	1.63E-01	4.776	2.827	9.11E-02	-0.029	0.024	2.26E-01
rs5762534	C	0.147	-1.609	3.300	6.26E-01	0.012	0.027	6.59E-01	-2.133	3.248	5.11E-01	0.013	0.027	6.33E-01
rs763121	G	0.343	-2.015	2.460	4.13E-01	-0.002	0.020	9.15E-01	-0.841	2.435	7.30E-01	-0.012	0.020	5.43E-01

Table S2_E: Data for the MR analyses on FEV_1 (GY).

For each SNP, estimates of the gene-Lung function outcomes (GY) are given for FEV_1. EA: effect allele; EAF: effect allele frequency; SE: standard errors of the related estimates; All analyses assumed an additive genetic model (per-allele genetic effect) and effect estimates are given in mL change for FEV_1. Sample size early menopause: 86,274 and late menopause: 87,536.

			Early menopause			Late menopause		
SNP	EA	EAF	GY	SE_GY	P_GY	GY	SE_GY	P_GY
rs4246511	C	0.701	0.855	2.190	6.96E-01	1.689	2.152	4.32E-01
rs12142240	C	0.306	-3.277	2.135	1.25E-01	-4.278	2.098	4.14E-02
rs1411478	G	0.596	-3.885	2.006	5.28E-02	-5.092	1.981	1.01E-02
rs2236918	G	0.548	-0.426	1.977	8.29E-01	-1.546	1.950	4.28E-01
rs1635501	T	0.527	-1.081	1.978	5.85E-01	-1.819	1.951	3.51E-01
rs2303369	T	0.393	-0.802	2.016	6.91E-01	-0.441	1.990	8.25E-01
rs704795	A	0.397	-0.070	2.014	9.72E-01	0.201	1.987	9.20E-01
rs1800932	G	0.193	-4.413	2.499	7.74E-02	-4.824	2.455	4.94E-02
rs10496265	C	0.176	2.608	2.589	3.14E-01	3.605	2.549	1.57E-01
rs930036	A	0.381	-2.731	2.021	1.76E-01	-2.625	1.995	1.88E-01
rs10183486	T	0.374	-3.508	2.026	8.34E-02	-3.864	2.001	5.35E-02
rs7606918	G	0.152	2.882	2.746	2.94E-01	3.547	2.716	1.91E-01
rs16858210	A	0.243	-6.643	2.307	3.98E-03	-7.713	2.270	6.79E-04
rs4693089	G	0.487	-1.475	1.961	4.52E-01	-3.186	1.935	9.97E-02
rs6856693	G	0.422	-3.999	1.986	4.41E-02	-3.881	1.958	4.75E-02
rs427394	G	0.415	2.541	1.993	2.02E-01	2.142	1.970	2.77E-01
rs11738223	G	0.333	0.309	2.093	8.83E-01	-0.567	2.061	7.83E-01
rs2241584	A	0.384	-1.646	2.042	4.20E-01	-1.105	2.016	5.84E-01
rs890835	C	0.888	1.122	3.116	7.19E-01	0.841	3.065	7.84E-01
rs691141	A	0.442	-1.353	1.994	4.97E-01	-1.722	1.961	3.80E-01
rs7718874	G	0.477	-1.266	1.978	5.22E-01	-1.292	1.948	5.07E-01
rs365132	T	0.477	-1.005	1.973	6.10E-01	-1.088	1.944	5.76E-01
rs402511	A	0.477	-1.176	1.972	5.51E-01	-1.191	1.943	5.40E-01
rs6899676	G	0.199	-1.192	2.479	6.31E-01	-2.705	2.428	2.65E-01
rs2153157	A	0.493	-0.762	1.964	6.98E-01	-1.061	1.935	5.84E-01
rs9393800	G	0.274	0.945	2.225	6.71E-01	0.487	2.205	8.25E-01
rs2230365	T	0.141	3.028	2.817	2.82E-01	2.804	2.766	3.11E-01
rs1046089	A	0.361	-7.162	2.047	4.67E-04	-8.170	2.024	5.45E-05
rs707938	G	0.324	-4.590	2.101	2.89E-02	-6.266	2.077	2.55E-03
rs12196873	C	0.144	0.075	2.801	9.79E-01	0.440	2.755	8.73E-01
rs2517388	G	0.173	1.081	2.605	6.78E-01	1.678	2.555	5.11E-01
rs2720044	C	0.163	0.666	2.682	8.04E-01	1.662	2.628	5.27E-01
rs10957156	A	0.753	-0.771	2.287	7.36E-01	-0.842	2.250	7.08E-01
rs4879656	A	0.378	1.598	2.018	4.28E-01	0.971	1.996	6.27E-01
rs10905065	A	0.606	-0.435	2.016	8.29E-01	0.304	1.986	8.79E-01
rs11031006	A	0.145	-2.390	2.806	3.94E-01	-2.036	2.756	4.60E-01
rs6484478	G	0.772	-3.993	2.341	8.80E-02	-2.010	2.311	3.84E-01
rs12294104	T	0.176	-2.516	2.590	3.31E-01	-2.014	2.547	4.29E-01
rs10734411	A	0.482	3.400	1.963	8.33E-02	4.260	1.939	2.81E-02
rs2277339	G	0.106	6.978	3.179	2.82E-02	8.085	3.179	1.10E-02
rs3741604	T	0.528	-2.410	1.978	2.23E-01	-1.942	1.949	3.19E-01
rs75770066	G	0.030	-9.704	5.864	9.79E-02	-5.908	5.563	2.88E-01
rs1183272	C	0.446	5.745	1.978	3.67E-03	5.814	1.950	2.87E-03

			Early menopause			*Late menopause*		
SNP	***EA***	***EAF***	***GY***	***SE_GY***	***P_GY***	***GY***	***SE_GY***	***P_GY***
rs7397861	G	0.633	-1.301	2.044	5.24E-01	-1.111	2.012	5.81E-01
rs551087	A	0.714	6.742	2.172	1.91E-03	7.721	2.142	3.13E-04
rs1727326	G	0.860	7.327	2.828	9.57E-03	7.179	2.802	1.04E-02
rs12824058	G	0.419	3.201	1.996	1.09E-01	3.461	1.974	7.96E-02
rs3736830	C	0.852	0.762	2.756	7.82E-01	1.024	2.725	7.07E-01
rs4886238	A	0.327	4.715	2.108	2.53E-02	3.934	2.074	5.78E-02
rs7333181	A	0.135	-1.024	2.882	7.22E-01	-3.514	2.838	2.16E-01
rs1713460	G	0.313	1.535	2.110	4.67E-01	1.991	2.084	3.39E-01
rs9796	T	0.473	6.060	1.975	2.15E-03	6.099	1.947	1.73E-03
rs2307449	G	0.391	3.765	2.010	6.10E-02	4.570	1.985	2.13E-02
rs1054875	T	0.393	4.243	2.016	3.53E-02	4.994	1.991	1.21E-02
rs9039	C	0.271	-2.507	2.224	2.60E-01	-3.275	2.196	1.36E-01
rs10852344	T	0.596	0.398	2.005	8.43E-01	1.329	1.978	5.02E-01
rs12599106	A	0.503	0.573	1.974	7.72E-01	1.197	1.950	5.39E-01
rs8070740	G	0.242	-3.556	2.304	1.23E-01	-2.320	2.267	3.06E-01
rs2941505	G	0.685	2.487	2.113	2.39E-01	3.062	2.086	1.42E-01
rs1799949	A	0.324	3.975	2.101	5.85E-02	3.676	2.066	7.51E-02
rs349306	A	0.872	2.776	2.996	3.54E-01	1.419	2.975	6.33E-01
rs7259376	G	0.535	1.902	1.972	3.35E-01	2.021	1.944	2.99E-01
rs12611091	C	0.490	0.558	1.960	7.76E-01	1.521	1.938	4.32E-01
rs1551562	G	0.234	-1.860	2.348	4.28E-01	-2.575	2.334	2.70E-01
rs1172822	T	0.376	0.354	2.027	8.61E-01	0.130	2.009	9.48E-01
rs7246479	G	0.514	-0.618	1.967	7.53E-01	-0.714	1.943	7.13E-01
rs2384687	G	0.398	0.373	2.009	8.53E-01	0.034	1.989	9.86E-01
rs11668344	G	0.364	1.313	2.038	5.19E-01	0.910	2.022	6.53E-01
rs897798	G	0.466	0.730	1.965	7.10E-01	0.617	1.946	7.51E-01
rs2547274	C	0.093	-7.351	3.435	3.24E-02	-5.490	3.371	1.03E-01
rs12461110	A	0.365	4.278	2.045	3.64E-02	3.721	2.019	6.53E-02
rs236114	C	0.796	4.077	2.446	9.55E-02	2.298	2.396	3.37E-01
rs451417	A	0.124	11.349	2.974	1.35E-04	8.166	2.958	5.76E-03
rs16991615	A	0.062	-4.567	4.178	2.74E-01	-3.784	3.967	3.40E-01
rs140267842	A	0.009	12.155	10.383	2.42E-01	9.314	10.046	3.54E-01
rs2236553	T	0.753	-1.608	2.302	4.85E-01	-0.224	2.281	9.22E-01
rs13040088	G	0.213	2.121	2.394	3.76E-01	2.485	2.372	2.95E-01
rs5762534	C	0.147	-2.157	2.771	4.36E-01	-2.779	2.725	3.08E-01
rs763121	G	0.343	-2.134	2.066	3.02E-01	-1.798	2.043	3.79E-01

Table S3_A. Results of main and secondary MR analyses on early/late menopause and of FEV_1/FVC.

*Pleiotropy = statistical evidence of pleiotropy: I^2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

	Early menopause							***Late menopause***						
	N	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***	***N***	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***
Observational analysis	77303	-	-0.19	-0.34	-0.03	**0.019**		78475	-	0.11	-0.04	0.25	0.139	
Main MR analysis														
IVW - Fixed-effect	86274	39	0.29	0.22	0.36	**1.48E-16**	*I^2= 48 [34-83]; het_P= $8.9x10^{-7}$*	87536	40	-0.18	-0.26	-0.1	**1.09E-05**	*I^2= 53 [44-84]; het_P= $5.2x10^{-10}$*
Other MR methods														
2SLS MR	86274	39	0.26	0.15	0.37	**3.89E-06**		87536	40	-0.15	-0.25	-0.05	**4.28E-03**	
IVW - Random-effect	86274	39	0.29	0.18	0.40	**1.75E-07**	*I^2= 48 [34-83]; het_P= $8.9x10^{-7}$*	87536	40	-0.18	-0.32	-0.04	**0.012**	*I^2= 53 [44-84]; het_P= $5.2x10^{-10}$*
Weighted median estimator	86274	39	0.35	0.22	0.48	**1.19E-07**		87536	40	-0.16	-0.31	-0.01	**0.039**	
MR Egger regression	86274	39	0.43	0.24	0.63	**8.19E-06**	*Intercept_P = 0.101*	87536	40	-0.08	-0.28	0.13	0.462	*Intercept_P = 0.249*
MR-PRESSO (raw)	86274	39	0.26	0.12	0.40	**9.92E-04**	*P_global = <0.0005; P_dis = 0.429*	87536	40	-0.14	-0.29	0.02	0.093	*P_global = <0.0005; P_dis = 0.620*
MR-PRESSO (corrected)	86274	39	0.31	0.21	0.40	**3.45E-07**	*Outliers: rs1411478, rs1800932, rs1046089, rs707938*	87536	40	-0.17	-0.29	-0.05	**8.20E-03**	*Outliers: rs1411478, rs1046089, rs707938*
Pleiotropy MR analyses														
Height SNPs excluded	86274	30	0.28	0.21	0.36	**2.29E-13**	*I^2= 56 [47-88]; het_P= $1.1x10^{-7}$*	87536	31	-0.22	-0.33	-0.11	**6.90E-05**	*I^2= 61 [49-86]; het_P= $5.3x10^{-11}$*
BMI SNPs excluded	86274	36	0.29	0.22	0.36	**1.93E-16**	*I^2= 50 [39-85]; het_P= $4.7x10^{-7}$*	87536	37	-0.17	-0.26	-0.09	**3.13E-05**	*I^2= 54 [44-85]; het_P= $4.7x10^{-10}$*
Menarche SNPs excluded	86274	36	0.29	0.22	0.36	**1.02E-14**	*I^2= 49 [34-84]; het_P= $1.4x10^{-6}$*	87536	37	-0.23	-0.33	-0.13	**7.32E-06**	*I^2= 56 [43-83]; het_P= $3.6x10^{-10}$*
All pleiotropic SNPs excluded	86274	28	0.29	0.22	0.37	**7.13E-14**	*I^2= 57 [49-89]; het_P= $1.7x10^{-7}$*	87536	28	-0.22	-0.33	-0.11	**1.33E-04**	*I^2= 61 [49-87]; het_P= $1.6x10^{-10}$*
Sensitivity MR analyses														
Women with complete data*	77303	39	0.28	0.21	0.35	**1.86E-14**	*I^2= 45 [25-80]; het_P= $8.9x10^{-6}$*	78475	40	-0.17	-0.25	-0.08	**9.63E-05**	*I^2= 53 [44-84]; het_P= $2.4x10^{-10}$*
Non-asthmatics	76367	39	0.31	0.24	0.38	**7.47E-18**	*I^2= 42 [19-80]; het_P= $1.1x10^{-4}$*	77562	40	-0.18	-0.26	-0.10	**1.79E-05**	*I^2= 53 [44-83]; het_P= $4.9x10^{-10}$*
Limit to Day et al. SNPs	86274	54	0.26	0.15	0.36	**8.03E-07**	*I^2= 20 [0-59]; het_P= 0.558*	87536	54	-0.17	-0.27	-0.07	**5.14E-04**	*I2= 25 [0-65]; het_P= 0.050*

Table S3_B. Results of main and secondary MR analyses on early/late menopause and of FEV_1/FVC < LLN.

*Pleiotropy = statistical evidence of pleiotropy: I^2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

	Early menopause							***Late menopause***						
	N	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***	***N***	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***
Observational analysis	77303	-	1.09	1.00	1.19	0.063		78475	-	0.92	0.84	1.02	0.101	
Main MR analysis														
IVW - Fixed-effect	86274	39	0.85	0.82	0.89	**5.88E-14**	*I^2= 16 [0-60]; het_P= 0.012*	87536	40	1.06	1.01	1.11	**0.018**	*I^2= 20 [0-58]; het_P= $3.2x10^{-4}$*
Other MR methods														
2SLS MR	86274	39	0.90	0.84	0.96	**1.86E-03**		87536	40	1.05	0.99	1.11	0.117	
IVW - Random-effect	86274	39	0.85	0.81	0.90	**2.45E-09**	*I^2= 16 [0-60]; het_P= 0.012*	87536	40	1.06	0.99	1.13	0.090	*I^2= 20 [0-58]; het_P= $3.2x10^{-4}$*
Weighted median estimator	86274	39	0.84	0.77	0.91	**1.16E-05**		87536	40	1.02	0.93	1.12	0.709	
MR Egger regression	86274	39	0.80	0.72	0.88	**1.19E-05**	*Intercept_P = 0.137*	87536	40	0.93	0.83	1.03	0.161	*Intercept_P = $3.9x10^{-3}$*
MR-PRESSO (raw)	86274	39	0.89	0.83	0.94	**2.79E-04**	*P_global = 0.074; P_dis = >0.05*	87536	40	1.05	0.98	1.12	0.163	*P_global = 0.052; P_dis = >0.05*
MR-PRESSO (corrected)							*No significant outliers*							*No significant outliers*
Pleiotropy MR analyses														
Height SNPs excluded	86274	30	0.84	0.81	0.88	**1.44E-13**	*I^2= 26 [0-70]; het_P= $5.7x10^{-3}$*	87536	31	1.10	1.03	1.17	**4.53E-03**	*I^2= 23 [0-60]; het_P= $6.4x10^{-4}$*
BMI SNPs excluded	86274	36	0.85	0.82	0.89	**7.60E-14**	*I^2= 19 [0-64]; het_P= $8.8x10^{-3}$*	87536	37	1.06	1.01	1.11	**0.027**	*I^2= 20 [0-59]; het_P= $3.8x10^{-4}$*
Menarche SNPs excluded	86274	36	0.84	0.81	0.88	**2.85E-14**	*I^2= 19 [0-63]; het_P= 0.011*	87536	37	1.11	1.04	1.17	**1.09E-03**	*I^2= 24 [0-57]; het_P= $5.2x10^{-4}$*
All pleiotropic SNPs excluded	86274	28	0.84	0.80	0.88	**1.19E-13**	*I^2= 30 [0-74]; het_P= $3.1x10^{-3}$*	87536	28	1.09	1.02	1.16	**0.015**	*I^2= 23 [0-61]; het_P= $5.2x10^{-4}$*
Sensitivity MR analyses														
Women with complete data*	77303	39	0.87	0.84	0.91	**7.14E-10**	*I^2= 14 [0-58]; het_P= 0.013*	78475	40	1.05	1.00	1.11	**0.042**	*I^2= 13 [0-51]; het_P= $1.4x10^{-3}$*
Non-asthmatics	76367	39	0.84	0.80	0.88	**2.07E-12**	*I^2= 7 [0-48]; het_P= 0.028*	77562	40	1.06	1.00	1.12	**0.044**	*I^2= 6 [0-48]; het_P= $2.1x10^{-3}$*
Limit to Day et al. SNPs	86274	54	0.90	0.82	0.96	**9.69E-04**	*I2= 0 [0-25]; het_P=0.777*	87536	54	1.06	1.00	1.12	0.058	*I2= 0 [0-24]; het_P=0.741*

Table S3_C. Results of main and secondary MR analyses on early/late menopause and of FVC.

*Pleiotropy = statistical evidence of pleiotropy: I^2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

	Early menopause							***Late menopause***						
	N	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***	***N***	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***
Observational analysis	77303	-	-36.32	-48.81	-23.82	**1.22E-08**		78475	-	2.87	-8.58	14.32	0.623	
Main MR analysis														
IVW - Fixed-effect	86274	39	-4.98	-10.49	0.53	0.077	*I^2= 46 [27-81]; het_P= $2.5x10^{-7}$*	87536	40	-7.10	-13.46	-0.75	**0.028**	*I^2= 46 [29-80]; het_P= $2.4x10^{-7}$*
Other MR methods														
2SLS MR	86274	39	0.70	-7.86	9.25	0.873		87536	40	-13.53	-21.38	-5.68	**7.32E-04**	
IVW - Random-effect	86274	39	-4.98	-13.87	3.92	0.273	*I^2= 46 [27-81]; het_P= $2.5x10^{-7}$*	87536	40	-7.10	-17.31	3.10	0.172	*I^2= 46 [29-80]; het_P= $2.4x10^{-7}$*
Weighted median estimator	86274	39	-10.70	-21.72	0.32	0.057		87536	40	-10.11	-21.16	0.95	0.073	
MR Egger regression	86274	39	-14.34	-29.74	1.06	0.068	*Intercept_P = 0.181*	87536	40	-15.35	-30.90	0.20	0.053	*Intercept_P = 0.224*
MR-PRESSO (raw)	86274	39	-3.00	-13.61	7.62	0.583	*P_global = <0.0005; P_dis = 0.684*	87536	40	-9.56	-20.34	1.22	0.090	*P_global = <0.0005; P_dis = 0.604*
MR-PRESSO (corrected)	86274	39	-5.62	-14.93	3.69	0.244	*Outliers: rs1800932, rs9796*	87536	40	-7.85	-18.13	2.42	0.142	*Outliers: rs9796*
Pleiotropy MR analyses														
Height SNPs excluded	86274	30	-7.12	-13.17	-1.08	**0.021**	*I^2= 45 [17-81]; het_P= $3.9x10^{-5}$*	87536	31	-0.25	-8.84	8.35	0.955	*I^2= 43 [12-75]; het_P= $5.6x10^{-5}$*
BMI SNPs excluded	86274	36	-4.09	-9.65	1.48	0.150	*I^2= 45 [22-80]; het_P= $7.4x10^{-7}$*	87536	37	-8.34	-14.82	-1.86	**0.012**	*I^2= 46 [27-80]; het_P= $4.7x10^{-7}$*
Menarche SNPs excluded	86274	36	-6.91	-12.76	-1.07	**0.020**	*I^2= 48 [31-82]; het_P= $2.3x10^{-7}$*	87536	37	-6.97	-14.86	0.91	0.083	*I^2= 50 [31-79]; het_P= $5.3x10^{-8}$*
All pleiotropic SNPs excluded	86274	28	-6.77	-12.86	-0.67	**0.030**	*I^2= 44 [13-81]; het_P= $2.5x10^{-5}$*	87536	28	-1.69	-10.60	7.22	0.710	*I^2= 43 [10-77]; het_P= $7.1x10^{-5}$*
Sensitivity MR analyses														
Women with complete data*	77303	39	-3.07	-8.83	2.68	0.295	*I^2= 42 [20-79]; het_P= $5.5x10^{-6}$*	78475	40	-7.92	-14.55	-1.30	**0.019**	*I^2= 40 [16-78]; het_P= $1.1x10^{-5}$*
Non-asthmatics	76367	39	-7.68	-13.51	-1.85	**0.010**	*I^2= 43 [19-79]; het_P= $9.5x10^{-7}$*	77562	40	-4.07	-10.78	2.64	0.235	*I^2= 50 [35-81]; het_P= $6.9x10^{-9}$*
Limit to Day et al. SNPs	86274	54	0.72	-7.36	8.80	0.861	*I^2= 34 [8-70]; het_P= $9.1x10^{-3}$*	87536	54	-9.96	-17.56	-2.35	**0.011**	*I^2= 33 [7-74]; het_P= 0.011*

Table S3_D. Results of main and secondary MR analyses on early/late menopause and of FVC < LLN.

*Pleiotropy = statistical evidence of pleiotropy: I^2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

	Early menopause							***Late menopause***						
	N	*N SNPs*	*Beta*	*LCL*	*UCL*	*P*	*Pleiotropy*	*N*	*N SNPs*	*Beta*	*LCL*	*UCL*	*P*	*Pleiotropy*
Observational analysis	77303	-	1.13	1.02	1.24	**0.016**		78475	-	0.98	0.89	1.08	0.636	
Main MR analysis														
IVW - Fixed-effect	86274	39	1.03	0.99	1.08	0.143	*I^2= 0 [0-50]; het_P= 0.098*	87536	40	1.00	0.95	1.05	0.970	*I^2= 18 [0-64]; het_P= $6.8x10^{-3}$*
Other MR methods														
2SLS MR	86274	39	0.98	0.92	1.05	0.629		87536	40	1.06	1.00	1.14	0.066	
IVW - Random-effect	86274	39	1.03	0.98	1.09	0.200	*I^2= 0 [0-50]; het_P= 0.098*	87536	40	1.00	0.93	1.07	0.976	*I^2= 18 [0-64]; het_P= $6.8x10^{-3}$*
Weighted median estimator	86274	39	1.06	0.98	1.15	0.154		87536	40	1.00	0.92	1.09	0.979	
MR Egger regression	86274	39	1.12	1.00	1.24	**0.041**	*Intercept_P = 0.113*	87536	40	0.97	0.86	1.08	0.556	*Intercept_P = 0.504*
MR-PRESSO (raw)	86274	39	1.02	0.96	1.08	0.602	*P_global = 0.224; P_dis = >0.05*	87536	40	1.03	0.96	1.10	0.454	*P_global = 0.047; P_dis = >0.05*
MR-PRESSO (corrected)							*No significant outliers*							*No significant outliers*
Pleiotropy MR analyses														
Height SNPs excluded	86274	30	1.04	0.99	1.09	0.167	*I^2= 10 [0-62]; het_P= 0.044*	87536	31	1.01	0.94	1.08	0.808	*I^2= 22 [0-68]; het_P= $7.2x10^{-3}$*
BMI SNPs excluded	86274	36	1.03	0.98	1.08	0.238	*I^2= 0 [0-43]; het_P= 0.174*	87536	37	1.00	0.95	1.06	0.938	*I^2= 12 [0-61]; het_P= 0.016*
Menarche SNPs excluded	86274	36	1.03	0.98	1.08	0.228	*I^2= 6 [0-55]; het_P= 0.055*	87536	37	1.04	0.97	1.11	0.253	*I^2= 20 [0-63]; het_P= $7.9x10^{-3}$*
All pleiotropic SNPs excluded	86274	28	1.03	0.98	1.08	0.268	*I^2= 2 [0-54]; het_P= 0.102*	87536	28	1.02	0.95	1.10	0.597	*I^2= 15 [0-66]; het_P= 0.021*
Sensitivity MR analyses														
Women with complete data*	77303	39	1.04	0.99	1.09	0.130	*I^2= 0 [0-46]; het_P= 0.160*	78475	40	0.99	0.94	1.05	0.812	*I^2= 16 [0-61]; het_P= 0.012*
Non-asthmatics	76367	39	1.05	1.00	1.10	0.065	*I^2= 4 [0-53]; het_P= 0.045*	77562	40	0.98	0.92	1.04	0.432	*I^2= 7 [0-50]; het_P= 0.029*
Limit to Day et al. SNPs	86274	54	0.98	0.91	1.04	0.457	*I^2= 0 [0-35]; het_P= 0.684*	87536	54	1.06	0.99	1.13	0.082	*I^2= 0 [0-42]; het_P= 0.504*

Table S3_E. Results of main and secondary MR analyses on early/late menopause and of FEV_1.

*Pleiotropy = statistical evidence of pleiotropy: I^2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

	Early menopause							Late menopause						
	N	*N SNPs*	*Beta*	*LCL*	*UCL*	*P*	*Pleiotropy*	*N*	*N SNPs*	*Beta*	*LCL*	*UCL*	*P*	*Pleiotropy*
Observational analysis	77303	-	-31.44	-41.97	-20.90	**4.95E-09**		78475	-	4.80	-4.85	14.45	0.330	
Main MR analysis														
IVW - Fixed-effect	86274	39	5.55	0.92	10.18	**0.019**	*I^2= 47 [33-82]; het_P= $1.3x10^{-6}$*	87536	40	-11.01	-16.34	-5.68	**5.14E-05**	*I^2= 46 [31-81]; het_P= $1.0x10^{-5}$*
Other MR methods														
2SLS MR	86274	39	8.67	1.43	15.90	**0.019**		87536	40	-14.48	-21.10	-7.85	**1.85E-05**	
IVW - Random-effect	86274	39	5.55	-1.72	12.82	0.135	*I^2= 47 [33-82]; het_P= $1.3x10^{-6}$*	87536	40	-11.01	-19.05	-2.98	**7.23E-03**	*I^2= 46 [31-81]; het_P= $1.0x10^{-5}$*
Weighted median estimator	86274	39	4.63	-4.01	13.26	0.294		87536	40	-10.15	-19.23	-1.07	**0.028**	
MR Egger regression	86274	39	2.28	-10.55	15.12	0.727	*Intercept_P = 0.576*	87536	40	-13.51	-26.21	-0.80	**0.037**	*Intercept_P = 0.653*
MR-PRESSO (raw)	86274	39	6.06	-2.91	15.02	0.193	*P_global = <0.0005; P_dis = 0.939*	87536	40	-11.53	-20.86	-2.20	**0.020**	*P_global = <0.0005; P_dis = 0.620*
MR-PRESSO (corrected)	86274	39	6.28	-1.60	14.16	0.127	*Outliers: rs1046089, rs451417*	87536	40	-14.58	-22.44	-6.73	**8.31E-04**	*Outliers: rs1046089, rs707938*
Pleiotropy MR analyses														
Height SNPs excluded	86274	30	3.89	-1.19	8.97	0.133	*I^2= 50 [34-85]; het_P= $1.0x10^{-5}$*	87536	31	-7.49	-14.70	-0.27	**0.042**	*I^2= 44 [18-79]; het_P= $4.0x10^{-4}$*
BMI SNPs excluded	86274	36	6.24	1.57	10.92	**8.84E-03**	*I^2= 47 [32-83]; het_P= $1.9x10^{-6}$*	87536	37	-11.69	-17.13	-6.25	**2.54E-05**	*I^2= 46 [31-83]; het_P= $1.3x10^{-5}$*
Menarche SNPs excluded	86274	36	4.17	-0.74	9.08	0.096	*I^2= 51 [39-84]; het_P= $7.4x10^{-7}$*	87536	37	-12.58	-19.20	-5.97	**1.93E-04**	*I^2= 50 [33-80]; het_P= $3.1x10^{-6}$*
All pleiotropic SNPs excluded	86274	28	4.35	-0.76	9.47	0.095	*I^2= 50 [33-86]; het_P= $1.4x10^{-5}$*	87536	28	-8.44	-15.92	-0.97	**0.027**	*I^2= 45 [18-81]; het_P= $4.5x10^{-4}$*
Sensitivity MR analyses														
Women with complete data*	77303	39	6.53	1.70	11.36	**8.06E-03**	*I^2= 46 [32-81]; het_P= $5.1x10^{-6}$*	78475	40	-11.21	-16.77	-5.66	**7.64E-05**	*I^2= 45 [31-83]; het_P= $5.3x10^{-6}$*
Non-asthmatics	76367	39	4.15	-0.68	8.98	0.092	*I^2= 40 [16-79]; het_P= $6.2x10^{-5}$*	77562	40	-8.77	-14.33	-3.21	**1.98E-03**	*I^2= 45 [27-80]; het_P= $1.7x10^{-5}$*
Limit to Day et al. SNPs	86274	54	8.87	2.07	15.66	**0.011**	*I^2= 33 [7-70]; het_P= 0.011*	87536	54	-12.98	-19.38	-6.58	**7.02E-05**	*I^2= 31 [4-74]; het_P= 0.017*

Table S4_A. Results of main and secondary MR analyses of lung function outcomes (FEV_1/FVC and FEV_1/FVC < LLN) and continuous age at menopause. *Pleiotropy = statistical evidence of pleiotropy: I2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

			FEV_1/FVC					***FEV_1/FVC < LLN***				
	N	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***	***OR***	***LCL***	***UCL***	***P***	***Pleiotropy***
Observational analysis	84844	-	0.02	0.01	0.03	**8.50E-06**		0.99	0.98	1.00	**9.25E-04**	
Main MR analysis												
IVW - Fixed-effect	94742	63	-0.09	-0.12	-0.06	**4.48E-09**	*I^2= 53 [40-76]; het_P=5.5x10^{-7}*	1.04	1.02	1.06	**6.85E-06**	*I^2= 17 [0-45]; het_P=6.0x10^{-3}*
Other MR methods												
2SLS MR	94742	63	-0.09	-0.13	-0.04	**2.15E-04**	Sargan = 2.4x10^{-6}	1.03	1.00	1.06	**3.86E-02**	
IVW - Random-effect	94742	63	-0.09	-0.14	-0.05	**5.87E-05**		1.04	1.02	1.07	**2.49E-04**	
Weighted median estimator	94742	63	-0.09	-0.16	-0.03	**3.35E-03**		1.04	1.00	1.08	**4.28E-02**	
MR Egger regression	94742	63	-0.10	-0.17	-0.03	**7.26E-03**	Intercept_P = 0.815	1.03	0.99	1.08	0.104	Intercept_P = 0.599
MR-PRESSO (raw)	94742	63	-0.08	-0.14	-0.02	**7.10E-03**	*P_global = <0.0005; P_dis = 0.478*	1.03	1.01	1.06	**8.43E-03**	*P_global = 0.077; P_dis = >0.05*
MR-PRESSO (corrected)	94742	63	-0.10	-0.14	-0.05	**4.06E-05**	*Outliers: rs1411478, rs1046089, rs707938*					*No significant outliers*
Pleiotropy analyses												
Height SNPs excluded	94742	47	-0.11	-0.14	-0.07	**1.45E-08**	*I^2= 59 [43-78]; het_P= 3.0x10^{-7}*	1.06	1.03	1.08	**6.67E-07**	*I^2= 21 [0-49]; het_P= 8.5x10^{-3}*
BMI SNPs excluded	94742	58	-0.09	-0.12	-0.06	**1.53E-08**	*I^2= 54 [41-77]; het_P= 7.2x10^{-7}*	1.04	1.02	1.06	**1.40E-05**	*I^2= 19 [0-47]; het_P= 4.5x10^{-3}*
Menarche SNPs excluded	94742	59	-0.10	-0.14	-0.07	**6.61E-09**	*I^2= 53 [36-74]; het_P= 6.4x10^{-7}*	1.06	1.03	1.08	**2.45E-07**	*I^2= 15 [0-42]; het_P= 1.2x10^{-2}*
All pleiotropic SNPs excluded	94742	43	-0.11	-0.15	-0.07	**2.20E-08**	*I^2= 60 [42-79]; het_P= 8.5x10^{-7}*	1.06	1.03	1.08	**1.60E-06**	*I^2= 23 [0-52]; het_P= 5.1x10^{-3}*
Sensitivity MR analyses												
Women with complete data*	84844	63	-0.09	-0.12	-0.05	**1.86E-07**	*I^2= 51 [38-75]; het_P= 1.8x10^{-6}*	1.04	1.02	1.06	**4.66E-04**	*I^2= 16 [0-46]; het_P= 9.5x10^{-3}*
Non-asthmatics	83842	61	-0.10	-0.13	-0.06	**2.24E-09**	*I^2= 52 [40-78]; het_P= 5.4x10^{-7}*	1.04	1.02	1.07	**7.76E-05**	*I^2= 4 [0-34]; het_P= 0.022*
Limit to Day et al. SNPs	94742	54	-0.09	-0.13	-0.05	**3.77E-05**	*I^2= 40 [17-69]; het_P=1.8x10^{-3}*	1.03	1.01	1.06	**1.30E-02**	*I^2= 2 [0-37]; het_P=0.431*
GX from Day et al.	94742	54	-0.10	-0.15	-0.06	**9.45E-06**	*I^2= 40 [18-69]; het_P=5.5x10^{-5}*	1.05	1.02	1.07	**1.30E-03**	*I^2= 0 [0-38]; het_P=0.277*

Table S4_B. Results of main and secondary MR analyses of lung function outcomes (FVC and FVC < LLN) and continuous age at menopause.

*Pleiotropy = statistical evidence of pleiotropy: I2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

			FVC					FVC < LLN				
	N	N SNPs	Beta	LCL	UCL	P	Pleiotropy	OR	LCL	UCL	P	Pleiotropy
Observational analysis	84844	-	2.25	1.40	3.11	**2.40E-07**		0.99	0.98	1.00	**7.70E-03**	
Main MR analysis												
IVW - Fixed-effect	94742	63	0.13	-2.32	2.58	0.917	*I^2= 51 [42-78]; het_P=1.3x10^{-9}*	1.00	0.98	1.02	0.828	*I^2= 23 [0-60]; het_P=4.9x10^{-3}*
Other MR methods												
2SLS MR	94742	63	-2.80	-6.34	0.75	0.122	Sargan = 1.2x10^{-6}	1.02	0.99	1.05	0.115	
IVW - Random-effect	94742	63	0.13	-3.71	3.97	0.947		1.00	0.97	1.02	0.861	
Weighted median estimator	94742	63	0.38	-4.51	5.27	0.878		0.98	0.94	1.02	0.279	
MR Egger regression	94742	63	4.13	-1.83	10.09	0.174	Intercept_P = 0.125	0.94	0.90	0.98	**7.81E-03**	Intercept_P = 2.3x10^{-3}
MR-PRESSO (raw)	94742	63	-0.42	-4.76	3.92	0.851	*P_global = <0.0005; P_dis = 0.034*	1.01	0.98	1.04	0.592	*P_global = 0.027; P_dis = >0.05*
MR-PRESSO (corrected)	94742	63	0.11	-4.13	4.35	0.961	*Outliers: rs1800932*					*No significant outliers*
Pleiotropy analyses												
Height SNPs excluded	94742	47	1.17	-1.76	4.10	0.434	*I^2= 45 [22-73]; het_P= 9.4x10^{-6}*	1.00	0.98	1.03	0.769	*I^2= 30 [0-67]; het_P= 2.0x10^{-3}*
BMI SNPs excluded	94742	58	-0.27	-2.76	2.22	0.833	*I^2= 52 [43-79]; het_P= 1.8x10^{-9}*	1.00	0.98	1.02	0.914	*I^2= 16 [0-56]; het_P= 1.7x10^{-2}*
Menarche SNPs excluded	94742	59	0.93	-1.83	3.70	0.509	*I^2= 54 [43-78]; het_P= 4.1x10^{-10}*	1.01	0.98	1.03	0.640	*I^2= 25 [0-60]; het_P= 3.3x10^{-3}*
All pleiotropic SNPs excluded	94742	43	0.92	-2.06	3.90	0.546	*I^2= 46 [23-76]; het_P= 8.9x10^{-6}*	1.01	0.98	1.03	0.657	*I^2= 22 [0-64]; het_P= 1.0x10^{-2}*
Sensitivity MR analyses												
Women with complete data*	84844	63	-0.11	-2.68	2.47	0.936	*I^2= 48 [37-77]; het_P= 6.7x10^{-8}*	0.99	0.97	1.02	0.575	*I^2= 23 [0-61]; het_P= 5.9x10^{-3}*
Non-asthmatics	83842	61	1.42	-1.16	4.00	0.282	*I^2= 49 [37-78]; het_P= 2.9x10^{-9}*	0.99	0.97	1.01	0.426	*I^2= 0 [0-52]; het_P= 0.013*
Limit to Day et al. SNPs	94742	54	-2.19	-5.49	1.11	0.194	*I^2= 53 [44-80]; het_P=3.6x10^{-6}*	1.02	1.00	1.05	0.106	*I^2= 25 [0-63]; het_P=0.057*
GX from Day et al.	94742	54	-2.30	-5.87	1.27	0.207	*I^2= 53 [44-79]; het_P=3.8x10^{-9}*	1.03	1.00	1.06	0.053	*I^2= 20 [0-56]; het_P=0.035*

Table S4_C. Results of main and secondary MR analyses of lung function outcomes (FEV_1) and continuous age at menopause.

*Pleiotropy = statistical evidence of pleiotropy: I2 [95%CI] and heterogeneity p-value (het_P) for the IVW method; p-value of the intercept of the regression line (Intercept_P) for MR-Egger regression; P_global= p-value for detection of horizontal pleiotropy; P_dis= p-value for difference between MR-PRESSO tests before and after correction for outliers. LCL and UCL: lower and upper confidence limits. *Women with complete data on all variables included in the observational analyses.*

			FEV_1				
	N	***N SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***
Observational analysis	84844	-	2.33	1.61	3.05	**2.43E-10**	
Main MR analysis							
IVW - Fixed-effect	94742	63	-2.91	-4.97	-0.86	**5.50E-03**	*I^2= 53 [45-79]; het_P=2.0x10^{-8}*
Other MR methods							
2SLS MR	94742	63	-4.81	-7.81	-1.81	**1.68E-03**	Sargan = 8.0x10^{-7}
IVW - Random-effect	94742	63	-2.91	-6.04	0.22	0.068	
Weighted median estimator	94742	63	-2.54	-6.31	1.23	0.187	
MR Egger regression	94742	63	-0.19	-5.12	4.75	0.941	Intercept_P = 0.207
MR-PRESSO (raw)	94742	63	-2.95	-6.65	0.74	0.123	*P_global = <0.0005; P_dis = 0.819*
MR-PRESSO (corrected)	94742	63	-3.30	-6.76	0.16	0.066	*Outliers: rs1046089, rs451417*
Pleiotropy analyses							
Height SNPs excluded	94742	47	-2.60	-5.06	-0.14	**3.82E-02**	*I^2= 50 [33-77]; het_P= 1.8x10^{-5}*
BMI SNPs excluded	94742	58	-3.14	-5.22	-1.05	**3.27E-03**	*I^2= 54 [47-81]; het_P= 2.3x10^{-8}*
Menarche SNPs excluded	94742	59	-2.68	-5.00	-0.36	**2.37E-02**	*I^2= 56 [46-79]; het_P= 3.5x10^{-9}*
All pleiotropic SNPs excluded	94742	43	-2.77	-5.27	-0.26	**3.05E-02**	*I^2= 51 [35-79]; het_P= 2.0x10^{-5}*
Sensitivity MR analyses							
Women with complete data*	84844	63	-2.88	-5.04	-0.72	**8.97E-03**	*I^2= 52 [44-79]; het_P= 1.8x10^{-7}*
Non-asthmatics	83842	61	-2.09	-4.24	0.05	0.055	*I^2= 48 [37-78]; het_P= 4.4x10^{-7}*
Limit to Day et al. SNPs	94742	54	-4.48	-7.25	-1.70	**1.58E-03**	*I^2= 51 [42-79]; het_P=1.2x10^{-5}*
GX from Day et al.	94742	54	-4.98	-7.97	-1.98	**1.13E-03**	*I^2= 54 [45-80]; het_P=3.7x10^{-9}*

Table S5. Results of subgroup MR analyses of lung function outcomes and age at menopause (Early versus Normal and Late versus Normal).

Pleiotropy = statistical evidence of pleiotropy: I^2 [95%CI] and heterogeneity p-value (het_P) for the IVW method. LCL and UCL: lower and upper confidence limits.

			FEV_1/FVC					**FEV_1/FVC < LLN**				
	N	***N_SNPs***	***Beta***	***LCL***	***UCL***	***P***	***Pleiotropy***	***OR***	***LCL***	***UCL***	***P***	***Pleiotropy***
Early vs Normal												
Smoking status												
Never-smokers	48857	39	0.29	0.20	0.37	**5.80E-11**	*I^2= 45 [26-81]; het_P= 9.7x10^{-6}*	0.83	0.78	0.88	**4.68E-09**	*I^2= 15 [0-60]; het_P= 0.026*
Ever-smokers	37438	39	0.26	0.14	0.37	**6.81E-06**	*I^2= 7 [0-59]; het_P= 0.252*	0.89	0.84	0.94	**1.94E-05**	*I^2= 0 [0-27]; het_P= 0.588*
			Interaction p-value = 0.642					*Interaction p-value = 0.102*				
HRT use												
Never-HRT users	49556	39	0.37	0.28	0.46	**3.51E-16**	*I^2= 28 [0-67]; het_P= 6.4x10^{-3}*	0.80	0.75	0.84	**2.35E-15**	*I^2= 14 [0-52]; het_P= 0.043*
Ever-HRT users	36718	39	0.23	0.12	0.34	**4.75E-05**	*I^2= 29 [0-75]; het_P= 5.1x10^{-3}*	0.91	0.86	0.97	**2.00E-03**	*I^2= 0 [0-48]; het_P= 0.209*
			Interaction p-value = 0.042					*Interaction p-value = 1.89x10^{-3}*				
Median current BMI												
BMI < 26	43680	39	0.46	0.36	0.56	**1.07E-19**	*I^2= 45 [22-79]; het_P= 9.2x10^{-7}*	0.82	0.78	0.87	**7.76E-13**	*I^2= 16 [0-60]; het_P= 7.9x10^{-3}*
BMI >= 26	42666	39	0.10	0.01	0.20	**0.033**	*I^2= 38 [11-77]; het_P= 6.8x10^{-5}*	0.90	0.85	0.96	**1.62E-03**	*I^2= 21 [0-68]; het_P= 0.013*
			Interaction p-value = 4.59x10^{-7}					*Interaction p-value = 0.026*				
Late vs Normal												
Smoking status												
Never-smokers	50217	40	-0.17	-0.27	-0.07	**7.29E-04**	*I^2= 42 [20-78]; het_P= 3.4x10^{-6}*	1.08	1.00	1.16	**0.042**	*I^2= 0 [0-46]; het_P= 0.060*
Ever-smokers	37338	40	-0.14	-0.27	-0.01	**0.031**	*I^2= 24 [0-65]; het_P= 0.024*	1.03	0.96	1.10	0.410	*I^2= 0 [0-35]; het_P= 0.204*
			Interaction p-value = 0.724					*Interaction p-value = 0.326*				
HRT use												
Never-HRT users	50745	40	-0.27	-0.37	-0.17	**2.90E-07**	*I^2= 36 [7-75]; het_P= 2.3x10^{-5}*	1.15	1.08	1.23	**3.61E-05**	*I^2= 16 [0-55]; het_P= 3.6x10^{-3}*
Ever-HRT users	36791	40	-0.12	-0.25	0.01	0.069	*I^2= 34 [2-74]; het_P= 2.0x10^{-3}*	1.00	0.93	1.07	0.916	*I^2= 0 [0-46]; het_P= 0.084*
			Interaction p-value = 0.073					*Interaction p-value = 4.04x10^{-3}*				
Median current BMI												
BMI < 26	43927	40	-0.30	-0.41	-0.18	**3.39E-07**	*I^2= 51 [39-83]; het_P= 1.1x10^{-12}*	1.10	1.04	1.18	**2.54E-03**	*I^2= 5 [0-49]; het_P= 3.3x10^{-3}*
BMI >= 26	43681	40	-0.07	-0.18	0.04	0.220	*I^2= 35 [5-73]; het_P= 6.5x10^{-4}*	1.01	0.94	1.09	0.839	*I^2= 21 [0-60]; het_P= 5.9x10^{-3}*
			Interaction p-value = 4.53x10^{-3}					*Interaction p-value = 0.070*				