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Is there a link between infertility, miscarriage, stillbirth, and premature or early menopause? Results from pooled analyses of nine cohort studies

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Tweetable statement: Women, especially Asian women, who experienced infertility, recurrent miscarriages, or recurrent stillbirths, were at higher risk of premature and early menopause.

Short title: infertility, miscarriage, stillbirth and premature or early menopause **AJOG at a Glance:**

A. Why was this study conducted?

- Women with premature or early menopause are at increased risk of menopausal symptoms, comorbidities, and all-cause mortality.
- There is little quantitative analysis of the association between infertility, miscarriage, stillbirth, and premature or early menopause. B. What are the key findings?
- A history of infertility, recurrent miscarriages (≥3), or recurrent stillbirths (≥2) was associated with higher risk of premature and early menopause.
- Asian women (mainly from East Asia) with infertility, recurrent miscarriages, or recurrent stillbirths had higher risk of premature and early menopause compared to nonAsian women with the same reproductive history. C. What does this study add to what is already known?
- The risk of premature and early menopause is higher among women, especially Asian women, with infertility, recurrent miscarriages or recurrent stillbirths.

Abstract

Background: Some reproductive factors (such as age at menarche and parity) have been shown to be associated with age at natural menopause, but there has been little quantitative analysis of the association between infertility, miscarriage, stillbirth, and premature (<40

years of age) or early menopause (40-44 years). Additionally, it was unknown whether the association would be different between Asian and non-Asian women, even though the age at natural menopause was younger among Asian women.

Objective: This study aimed to investigate the association of infertility, miscarriage, and stillbirth with age at natural menopause, and whether the association differed by race (Asian and non-Asian).

Study design: This was a pooled individual participant data analysis from nine observational studies, contributing to the InterLACE consortium. Naturally postmenopausal women with data on at least one of the reproductive factors (i.e., infertility, miscarriage, and stillbirth), age at menopause, and confounders (i.e., race, education level, age at menarche, body-mass index, and smoking status) were included. Multinominal logistic regression model was used to estimate relative risk ratios (RRRs) and 95% confidence intervals (CIs) for the association of infertility, miscarriage, and stillbirth with premature or early menopause, adjusting for confounders. Between study difference and within-study correlation were taken into account by including study as a fixed effect and indicating study as a cluster variable. We also examined the association with number of miscarriages (0, 1, 2, ≥3) and stillbirths (0, 1, ≥2) and tested whether the strength of association differed between Asian and non-Asian women.

Results: A total of 303,594 postmenopausal women were included. Their median age at natural menopause was 50.0 years (interquartile range: 47.0 – 52.0). The percentages of women with premature and early menopause were 2.1% and 8.4%, respectively. The RRRs (95%CIs) of premature and early menopause were 2.72 (1.77, 4.17) and 1.42 (1.15, 1.74) for women with infertility; 1.31 (1.08, 1.59) and 1.37 (1.14, 1.65) for women with recurrent miscarriages; and 1.54 (1.52, 1.56) and 1.39 (1.35, 1.43) for women with recurrent stillbirths. Asian women with infertility, recurrent miscarriages (≥3), or recurrent stillbirths (≥2) had

higher risk of premature and early menopause compared to non-Asian women with the same reproductive history.

Conclusion: The histories of infertility, recurrent miscarriages and stillbirths were associated early menopause

Introduction

Menopause is the permanent cessation of menstruation following the loss of ovarian follicular activity, which is diagnosed after 12 months of amenorrhoea.[1] The average age at menopause is about 51 years in Caucasian women, and 48-49 years in Asian women.[1–3] Menopause prior to 40 years is defined as premature menopause, and menopause between 40 and 45 years is called early menopause.[4] Women with premature or early menopause are at increased risk of menopause symptoms and non-communicable diseases, like cardiovascular disease, osteoporosis, cognitive decline, and all-cause mortality.[5–7]

Some reproductive factors (e.g., age at menarche and parity) and health factors [e.g., smoking and body-mass index (BMI)] influence age at natural menopause.[8–10] However, there has been little quantitative analysis of the association between infertility, miscarriage, stillbirth, and premature or early menopause. These reproductive histories are usually accompanied by sex hormone changes (e.g., low estrogen level) and associated with lifestyle factors (e.g., smoking and diet), which would contribute to earlier age at menopause.[8,11–14] It is plausible to hypothesise that these reproductive histories would be associated with the risk of premature and early menopause. In addition, Asian women experience menopause at younger age and have higher risk of premature and early menopause. Racial difference may exist in the associations of infertility, miscarriage, and stillbirth with age at natural menopause, which have not been explored in previous studies.[2,3]

In this study, pooled individual data from nine studies contributing to the International Collaboration for a Life Course Approach to Reproductive Health and Chronic Disease Events (InterLACE) consortium were used. The aim was to assess: 1) the associations of infertility, miscarriage, and stillbirth with age at natural menopause, and 2) whether the associations differed by race.

Materials and Methods

Data source and participants

The InterLACE is an individual-level pooled study of 27 observational studies, including over 850,000 women from 12 countries. Nine of these studies had data on at least one of the reproductive histories (i.e., infertility, miscarriage, and stillbirth), and age at menopause. They were Australian Longitudinal Study on Women's Health 1946-51 cohort (ALSWHmid), the Swedish Women's Lifestyle and Health Study (WLH), UK MRC National Survey of Health and Development (NSHD), the National Child Development Study (NCDS), the UK Women's Cohort Study (UKWCS), Japan Nurses' Health Study (JNHS), UK Biobank, China Kadoorie Biobank, and the Dutch Prospect-EPIC Utrecht in the European Prospective Investigation into Cancer and Nutrition (Prospect-EPIC). These studies started between 1990 and 2010 and recruited women at mid-life, except NSHD and NCDS, for which women were recruited from birth (Table S1). In present analysis, baseline was considered as study entry for most studies. To make the baseline comparable, survey 6 was selected as baseline for NSHD and NCDS when women were 43 and 42 years old, respectively. Women who experienced natural menopause and had data on at least one of the reproductive histories (i.e., infertility, miscarriage, and stillbirth), age at menopause, and potential confounders [race, education level, age at menarche, BMI, and smoking status] were included (Figure S1).

Reproductive histories

Information on infertility, miscarriage, and stillbirth was retrospectively collected through questionnaires at baseline or follow-up surveys (Table S2). Women provided information according to their understanding of their reproductive histories including diagnosis or treatment by physicians. Women were considered to have infertility, if they reported an experience of failing to establish a pregnancy after 12 months of regular, unprotected sexual

intercourse, consulting for infertility, being diagnosed with infertility, or receiving fertility treatment. Additionally, women self-reported outcome of each pregnancy (i.e., live birth, miscarriage, or stillbirth). The numbers of miscarriages and stillbirths were categorized into four groups (0, 1, 2, and ≥3) and three groups (0, 1, and ≥2) respectively. The histories of ≥3 miscarriages and ≥2 stillbirths were defined as recurrent miscarriages and recurrent stillbirths respectively, which could be interspersed with livebirths.[15] Age at natural menopause was retrospectively and prospectively collected at multiple surveys, and categorized as <40 (premature menopause), 40-44 (early menopause), 45-49, 50-51 (reference category), and ≥52 years.

Baseline characteristics

Information on race (Asian, Caucasian, and others), education level (≤10, 11-12, and >12 years), smoking never, monthly, weekly, and daily for Asian women;[16] <18.5, 18.5-24.9, 25.0-29.9, and ≥30 kg/m^2 for Caucasian and other women[17]), age at menarche (<11, 11-12, 13-14, and ≥15 years), and number of children (0, 1-2, and ≥3) was collected at baseline, while WLH collected data on alcohol intake in survey 2 and NCDS collected data on smoking status and alcohol intake in surveys 7 and 8. Caucasian women were mainly from Australia, Europe, and North America, and Asian women were mainly from East Asia.

Statistical analysis

Baseline characteristics were presented as numbers and percentages for categorical variables, and as median and interquartile range (IQR) for continuous variables. Observations in each included study were independent, and the dependent variable (age at natural menopause: <40, 40-44, 45-49, 50-51, and ≥52) had mutually exclusive categories. Multinominal (polytomous) logistic regression models were used to evaluate the associations of infertility, miscarriage, and

stillbirth with age at natural menopause. Multicollinearity among independent variables was assessed using variance inflation factors. All models were adjusted for potential confounding factors (race, education level, age at menarche, smoking status, and BMI).[8,11–13] Alcohol intake was included in a sensitivity analysis because this variable was not available in NSHD. Relative risk ratios (RRRs) and 95% confidence intervals (CIs) were estimated. Study was treated as a covariate and within-study correlation were taken into account by indicating study as a cluster variable. Analyses for miscarriage and stillbirth were restricted to women who had ever been pregnant. The interaction effect between fertility issues and Asian heritage (yes and no) was tested. The interaction effect was considered important, if the RRR for Asian women differed by 20% or more from the reference group, non-Asian women. In this case, categories of the fertility variable and Asian heritage were combined into single variable to estimate their associations with age at natural menopause.[18]

Several sensitivity analyses were conducted. First, analysis with additional adjustment of number of children was conducted, given the association between parity and age at natural menopause.[19] Second, models were additionally adjusted for alcohol intake, excluding NSHD for which alcohol data were not available. Third, one-year and two-year younger cutoff points were used to recategorize age at natural menopause among Asian women, given their higher rates of premature menopause (Asian vs non-Asian: 2.5% vs 1.7%) and early menopause (Asian vs non-Asian 9.7% vs 6.9%). This made the rates of premature and early menopause more comparable between Asian and non-Asian women. Fourth, E-values were used to assess the robustness of observed associations to unmeasured confounders.[20] This method has been proposed to quantify the minimum strength of the association that an unmeasured confounder or groups of confounders must have with both exposure and outcome to negate the observed association in observational studies.[21] All tests of statistical

hypotheses were done on the two-sided 5% level of significance, corresponding to RRR entirely within two-sided 95% confidence intervals. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC; procedure GEE for multinomial logistic regression). Computer codes are available from corresponding author by request.

Ethical statement

Each study in the InterLACE received ethics approval from the National Health Service research ethnics committee, the Human Research Ethics Committee or the Institutional Review Board at each study institution. All the participants provided informed consent or implied consent (demonstrating consent by returning questionnaire with contact detail in UKWCS).

Results

Overall, 303,594 postmenopausal women were included, and their median (IQR) age at natural menopause was 50.0 (47.0, 52.0) years. Among these women, 6,419 (2.1%) experienced premature menopause, and 25,440 (8.4%) experienced early menopause. Among the included women, 44,727, 279,305, and 268,346 women had data on infertility, miscarriage, and stillbirth respectively, and 4,317 (9.7%), 48,755 (17.5%), and 16,478 (6.1%) women experienced infertility, miscarriage, and stillbirth. Baseline characteristics of the included women are presented in Table 1. Due to missing values, 13.8% of the women were excluded from the analyses of infertility and they were more likely to be less educated (≤10 years, Figure S1, Table S3). In the analyses of miscarriage and stillbirth, 3.9% and 2.8% women with missing data were excluded respectively, and they were more likely to have more education (>12 years), younger age at menarche (<11 or 11-12 years), and 1-2 children.

Infertility

Compared to women without infertility, women with infertility had increased risk of premature menopause (RRR=2.72, 95%CI: 1.77-4.17) and early menopause (RRR=1.42, 95%CI: 1.15-1.74) rather than menopause at 50-51 years (Table 2). Asian women with infertility had higher risk of premature menopause, compared to non-Asian women with infertility, and possibly early menopause (Figure 1A).

Miscarriage

Among women who had ever been pregnant, compared to women without miscarriage and menopause age at 50-51, the risk of premature and early menopause increased with the number of miscarriages (1, 2, and ≥3), with the RRRs (95%CIs) of premature menopause increasing from 1.03 (1.01, 1.05) to 1.31 (1.08, 1.59) and the RRRs (95%CIs) of early menopause increasing from 1.06 (1.06, 1.07) to 1.37 (1.14, 1.65) (Table 2). Asian women with miscarriage, especially recurrent miscarriages, were at higher risk of premature and early menopause, compared to non-Asian women with same number of miscarriages (Figure 1B).

Stillbirth

Among women who had ever been pregnant, a history of stillbirth, especially recurrent stillbirths, was associated with higher risk of premature and early menopause (recurrent stillbirths: RRR=1.54, 95%CI: 1.52-1.56 and RRR=1.39, 95%CI: 1.35-1.43, Table 2), compared to women without stillbirth and menopause age at 50-51. Asian women who experienced stillbirth, especially recurrent stillbirths, were at higher risk of premature and early menopause, compared to non-Asian women with same stillbirth history (Figure 1C).

Sensitivity analyses

First, additional adjustment of number of children produced similar results to the main analysis, although the RRRs decreased slightly (Table S4, Figure S2). Second, additional adjustment of alcohol intake did not change the results (Table S5, Figure S3). Third, after reclassifying age at natural menopause among Asian women, infertility, recurrent miscarriages, and recurrent stillbirths were still associated with premature and early menopause (Table S6). Fourth, E-value calculations revealed that the assumption of unmeasured confounding needed to be at least 4.87 and 2.19 on the scale of RRR to negate the observed association of infertility with premature and early menopause, respectively. (Table S7) These E-value results suggested that the associations between recurrent miscarriages, recurrent stillbirths, and premature or early menopause were more vulnerable to unmeasured confounders.

Associations of infertility, miscarriage, and stillbirth, with age at menopause in each study are provided in Tables S8-S10. Variance inflation factor indicated no multicollinearity among explanatory variables (Table S11). Association for two or more miscarriages was provided for comparison among studies with different definitions on recurrent miscarriages (Table S12 and Figure S4).[22]

Comment

Principal findings

This pooled analysis revealed that reproductive histories of infertility, recurrent miscarriages and stillbirths, were associated with higher risk of premature and early menopause. The associations differed by race. Asian women with infertility, recurrent miscarriages, or recurrent stillbirths had higher risk of premature and early menopause compared to non-Asian women with the same reproductive history.

Results in the context of what is known

Although premature ovarian insufficiency as a cause of female infertility commonly leads to premature menopause, there has been little quantitative analysis of the relationship between infertility and premature or early menopause.[23,24] The study of Kok et al. selected 2393 women from the Prospect-EPIC study, who experienced natural menopause, and never used oral contraception or intra-uterine device, and found that for every five years later menopause, the odds of consulting physician for fertility problems was lower by 18% [odds ratio (OR)=0.82, 95%CI: 0.71-0.95].[25] Another study by Yasui et al. analysed the data of 24,153 pre- and postmenopausal women from JNHS, and revealed the association of onset of menopause with past history of infertility [age-adjusted OR (95%CI): 1.22 (1.04-1.44).[26] Present study pooled individual level data from these two studies and five additional studies, and found that women with infertility had almost three times higher risk of premature menopause, while the risk of early menopause was 42% higher. This finding was consistent with previous studies, and the association with premature menopause might be largely explained by premature ovarian insufficiency. Additionally, in the present study, the association between infertility and premature menopause was stronger among Asian women, indicating the existence of racial difference, which might be partly explained by differences in the causes of infertility. For example, Asian women have been reported to have a higher prevalence of endometriosis, and infertility due to endometriosis is more strongly associated with earlier menopause than infertility due to ovulation or tubal factors.[26,27] However, the present study was not able to assess this hypothesis due to the limited data on the causes of infertility.

In the present study, miscarriage and stillbirth were associated with an increased risk of premature and early menopause. Similarly, Kok et al.'s study from Prospect-EPIC revealed lower odds of miscarriage (OR=0.89, 95%CI: 0.79-1.01) associated with every five years later menopause.[25] The present study further explored the risk of premature and early

menopause among women with different numbers of miscarriages and stillbirths. Women who had experienced recurrent miscarriages or stillbirths were found at higher risk of premature and early menopause. This finding suggested that the underlying mechanisms linking miscarriage, stillbirth, and earlier age at natural menopause, might be more prevalent among women with recurrent miscarriages or stillbirths. The analysis also revealed that the associations differed by race, but little is known about the underlying mechanisms.[2,3,28,29]

Clinical implication

The present study supported the hypothesis that women with a history of infertility, recurrent miscarriages or stillbirths were at higher risk of premature and early menopause. There are a few mechanisms proposed. First, estrogen and progesterone are involved in ovulation, implantation and maintaining pregnancy, as well as menopause.[30,31] Women with infertility, miscarriage, or stillbirth may experience inadequate secretion of estrogen or progesterone.[32–36] In addition to the age-related decline in sex hormone, these fertility problems might put women at greater risk of earlier menopause. Second, ovarian reserve is diminished among women with such reproductive histories, accompanied by decreasing oocyte quality.[37–39] Women with infertility, miscarriage, or stillbirth may have lower levels of antimüllerian hormone and antral follicle count, which are associated with the quantity and quality of ovarian follicle pool.[40–42] The decreasing follicle pool would contribute to the accelerated progress of the menopause transition. Additionally, autoimmune disorders may play a role in the association, if ovarian or thyroid autoantibodies are more prevalent among women with infertility, pregnancy loss, and premature menopause.[43,44] Other factors associated with infertility and pregnancy loss, such as smoking, underweight, and depression, could also contribute to earlier age at menopause through cytotoxic effects on oocytes and granulosa cells, hypogonadotropic hypogonadism, and declining estrogen level.[8,45]

This study provided robust evidence for future clinical practice and guidelines. Early monitoring of menopausal symptom should be recommended for women who had experienced infertility, recurrent miscarriages or stillbirths. For women with such fertility issues, timely advice and management could reduce the impact of menopausal symptoms and comorbidities associated with premature or early menopause.

Research implications

The proposed underlying mechanisms are based on limited observational studies. Molecular studies are needed to reveal the exact biological mechanisms, linking infertility, miscarriage, stillbirth, and age at menopause. For the present study which suggested racial difference in the associations, the Asian women were mainly from China Biobank and JNHS, and the Caucasian women were mainly from UK Biobank. Future studies pooling data from other studies and other countries are needed to confirm this finding, and examine factors (e.g., biological or genetic factors) that might explain the racial differences.

Strengths and limitations

The present study had several strengths. As far as we know, this is the first study assessing the association of infertility, recurrent miscarriages, and recurrent stillbirths, with both premature and early menopause. It is based on individual-level data from divergent geographical regions which enhances the generalizability of study findings. Besides, the large sample size assured adequate power to detect the association of rare events (e.g., recurrent miscarriages and recurrent stillbirth) with premature or early menopause, and racial differences.

Several limitations need to be acknowledged. First, the histories of infertility, miscarriage, and stillbirth were self-reported, as well as age at menopause, which might have introduced recall bias. However, according to previous studies, self-reported histories of infertility

(sensitivity=72.0%, specificity=70.0%), pregnancy loss (sensitivity=73.5%, specificity=99.4%), and age at menopause (reproducibility: 72.5%-82.0%) would be reliable.[46–49] Second, due to limited data, the causes or treatments of these fertility issues could not be explored, and female and male infertility could not be separated. Third, the baseline characteristics were all collected at mid-life, and risk factor levels during reproductive age (e.g., BMI and smoking) were not available. Fourth, there might be unmeasured confounders, but the E-value calculation shows it was unlikely they would explain away the observed associations. Fifth, sample bias might exist. Overall, 397,953 women without natural menopause were excluded, of whom 319,972 women were at pre- or peri-menopause and 77,981 had experienced hysterectomy or oophorectomy. Besides 33,872 women were excluded due to missing data, and these women were more likely to be better educated (>12 years), experience earlier age at menarche (<11 years) and have no children. In addition, China Biobank and UK Biobank contributed the largest study populations, and they were not representative of the general populations. China Biobank participants were recruited from regions with high rates of certain conditions (e.g., stroke), and UK Biobank participants were healthier than the general population.[50,51]

Conclusions

Infertility, recurrent miscarriages and stillbirths were associated with higher risk of premature and early menopause, and the associations differed by race (Asian and non-Asian), with stronger associations for Asian women with such reproductive histories. This study extends current knowledge and suggests these reproductive histories as risk factors for premature and early menopause. Future cohort studies with data on causes and treatment of infertility or pregnancy loss are needed to shed more light on the associations, and molecular studies are required to reveal the exact biological mechanisms.

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Author contributions

Chen Liang: conceptualization, methodology, formal analysis, writing-original draft, writing-review & editing; **Hsin-Fang Chung:** methodology, writing-review & editing, supervision; **Annette J. Dobson**: methodology, writing-review & editing, supervision**; Janet E. Cade, Darren C. Greenwood, Yvonne T. van der Schouw, Rebecca Hardy, Diana Kuh, Kunihiko Hayashi, Sven Sandin, Elisabete Weiderpass**,: resources, writing-review & editing; **Gita D. Mishra**: conceptualization, methodology, writing-review & editing, supervision, project administration, funding acquisition.

Supplementary

Figure S1-S4

Table S1-S12

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Table 1. Baseline characteristics between women with and without a history of infertility, miscarriage, or stillbirth

Characteristics	Infertility (7 studies, N=44,727)		Miscarriage (7studies, N=279,305)		Stillbirth (5 studies, N=268,346)	
No. (%)	Never	Ever	Never	Ever	Never	Ever
Sample size						
	40,410 (90.35)	4,317 (9.65)	230,550 (82.54)	48,755 (17.46)	251,868 (93.86)	16,478 (6.14)
Race						
Caucasian	32,296 (79.92)	3,234 (74.91)	97,582 (42.33)	31,311 (64.22)	114,514 (45.47)	3,650 (22.15)
Asian	8,001 (19.80)	1,073 (24.86)	131,261 (56.93)	16,794 (34.45)	135,262 (53.70)	12,655 (76.80)
Other	113 (0.28)	10 (0.23)	1,707 (0.74)	650 (1.33)	2,092 (0.83)	173 (1.05)
Education level, years						
≤10	14,519 (35.93)	1,191 (27.59)	169,320 (73.44)	30,789 (63.15)	180,371 (71.61)	14,370 (87.21)
11-12	7,592 (18.79)	711 (16.47)	24,037 (10.43)	5,391 (11.06)	27,073 (10.75)	885 (5.37)
>12	18,299 (45.28)	2,415 (55.94)	37,193 (16.13)	12,575 (25.79)	44,424 (17.64)	1,223 (7.42)
Smoking status						
Past/non-smoker	33,577 (83.09)	3,458 (80.10)	213,794 (92.73)	44,443 (91.16)	233,245 (92.61)	15,308 (92.90)
Current smoker	6,833 (16.91)	859 (19.90)	16,756 (7.27)	4,312 (8.84)	18,623 (7.39)	1,170 (7.10)
Body-mass index, kg/m^2						
<18.5	867 (2.15)	133 (3.08)	7,594 (3.29)	1,372 (2.81)	7,665 (3.04)	1,123 (6.82)

18.5-24.9	23,237 (57.50)	2,728 (63.19)	86,657 (37.59)	19,197 (39.37)	93,151 (36.98)	6,495 (39.42)
25.0-29.9	12,257 (30.33)	1,087 (25.18)	93,513 (40.56)	18,690 (38.33)	102,782 (40.81)	6,299 (38.23)
≥30.0	4,049 (10.02)	369 (8.55)	42,786 (18.56)	9,496 (19.48)	48,270 (19.16)	2,561 (15.54)
Age at menarche, years						
<11	1,161 (2.87)	116 (2.69)	4,113 (1.78)	1,468 (3.01)	4,854 (1.93)	196 (1.19)
11-12	13,330 (32.99)	1,537 (35.60)	38,608 (16.75)	11,673 (23.94)	44,838 (17.80)	1,690 (10.26)
13-14	19,660 (48.65)	2,101 (48.67)	72,079 (31.26)	17,892 (36.70)	80,917 (32.13)	4,006 (24.31)
≥15	6,259 (15.49)	563 (13.04)	115,750 (50.21)	17,722 (36.35)	121,259 (48.14)	10,586 (64.24)
Number of children						
0	4,601 (11.56)	894 (21.25)	2,918 (1.27)	2,144 (4.40)	4,523 (1.80)	272 (1.65)
1-2	20,803 (52.28)	2,422 (57.56)	130,445 (56.60)	23,975 (49.24)	142,526 (56.59)	5,913 (35.90)
≥3	14,384 (36.15)	892 (21.20)	97,122 (42.14)	22,568 (46.35)	104,799 (41.61)	10,286 (62.45)

Women from seven studies (i.e., ALSWH-mid, WLH, NSHD, NCDS, UKWCS, JNHS, and Prospect-EPIC), seven studies (i.e., ALSWH-mid, NSHD, NCDS, UKWCS, UK Biobank, China Biobank, and Prospect-EPIC), and five studies (i.e., NSHD, NCDS, UK Biobank, China Biobank, and Prospect-EPIC) had data on infertility, miscarriage, and stillbirth, respectively. Body-mass index was categorized as <18.5, 18.5-22.9, 23.0-27.4, ≥27.5 kg/m^2 for Asian women, and as <18.5, 18.5-24.9, 25.0-29.9, and ≥30 kg/m^2 for other women.

Table 2. The association of infertility, miscarriage, and stillbirth with age at natural menopause

	Age at menopause, No.(%)					Adjusted RRR (95%CI)			
	<40	40-<45	45-<50	50-51	≥52	<40	40-<45	45-<50	≥52
History of infertility									
Never	649 (1.61)	2,415 (5.98)	10,814 (26.76)	9,968 (24.67)	16,564 (40.99)	1.00	1.00	1.00	1.00
Ever	112 (2.59)	276 (6.39)	1,214 (28.12)	988 (22.89)	1,727 (40.00)	2.72 (1.77,4.17)	1.42 (1.15,1.74)	1.19 (1.03,1.36)	1.00 (0.91,1.09)
History of miscarriage									
Never	5,080 (2.20)	19,955 (8.66)	77,556 (33.64)	54,350 (23.57)	73,609 (31.93)	1.00	1.00	1.00	1.00
Ever	1,006 (2.06)	4,198 (8.61)	14,288 (29.31)	11,291 (23.16)	17,972 (36.86)	1.06 (1.01,1.10)	1.11 (1.08,1.14)	1.02 (1.00,1.03)	1.03 (0.98,1.07)
Number of miscarriages									
0	4,919 (2.17)	19,603 (8.66)	76,415 (33.76)	53,335 (23.57)	72,051 (31.84)	1.00	1.00	1.00	1.00
1	687 (1.97)	2,918 (8.36)	10,286 (29.47)	8,146 (23.34)	12,862 (36.85)	1.03 (1.01,1.05)	1.06 (1.06,1.07)	1.00 (0.98,1.02)	1.03 (0.98,1.07)
2	175 (2.14)	729 (8.92)	2,354 (28.80)	1,846 (22.59)	3,069 (37.55)	1.17 (1.07,1.28)	1.18 (1.08,1.29)	1.03 (1.01,1.06)	1.06 (1.00,1.13)
≥3	88 (2.31)	380 (9.98)	1,118 (29.37)	851 (22.35)	1,370 (35.99)	1.31 (1.08,1.59)	1.37 (1.14,1.65)	1.12 (1.07,1.16)	0.98 (0.92,1.05)
History of stillbirth									
Never	5,350 (2.12)	21,552 (8.56)	83,407 (33.12)	59,225 (23.51)	82,334 (32.69)	1.00	1.00	1.00	1.00
Ever	466 (2.83)	1,806 (10.96)	5,752 (34.91)	3,836 (23.28)	4,618 (28.03)	1.15 (1.11,1.19)	1.15 (1.11,1.19)	0.92 (0.86,0.98)	1.03 (1.02,1.05)
Number of stillbirths									
0	5,350 (2.12)	21,552 (8.56)	83,407 (33.12)	59,225 (23.51)	82,334 (32.69)	1.00	1.00	1.00	1.00

1	322 (2.54)	1,305 (10.30)	4,379 (34.55)	3,005 (23.71)	3,662 (28.90)	1.04 (0.97,1.11)	1.08 (1.02,1.15)	0.91 (0.86,0.97)	1.02 (1.01,1.02)
≥2	144 (3.79)	501 (13.20)	1,371 (36.13)	829 (21.84)	950 (25.03)	1.54 (1.52,1.56)	1.39 (1.35,1.43)	0.95 (0.87,1.04)	1.09 (1.01,1.17)

RRR: relative risk ratio. CI: confidence interval. Women from seven studies (i.e., ALSWH-mid, WLH, NSHD, NCDS, UKWCS, JNHS, and Prospect-EPIC), seven studies (i.e., ALSWH-mid, NSHD, NCDS, UKWCS, UK Biobank, China Biobank, and Prospect-EPIC), and five studies (i.e., NSHD, NCDS, UK Biobank, China Biobank, and Prospect-EPIC) were included in the analysis for infertility, miscarriage, and stillbirth, respectively. Models were adjusted for race, education level, age at menarche, body-mass index, and smoking status. Study variability and within-study correlation were taken into account by including study as a covariate and indicating study as cluster variable in all models.

Figure 1. The association of infertility, miscarriage, and stillbirth with premature or early menopause among Non-Asian and Asian women

Race	Infertility	Premature menopause RRR (95%CI)	Early menopause RRR (95%CI)
Non-Asian	Never	1.00	1.00
	Ever	2.39 (1.58,3.61)	1.32 (1.11,1.58)
Asian	Never	2.20 (1.00,4.86)	1.08 (0.60,1.95)
	Ever	9.28 (4.13,20.85)	1.98 (1.09,3.59)

(A)

Race	Miscarriage	Premature menopause RRR (95%CI)	Early menopause RRR (95%CI)
Non-Asian	Never	1.00	1.00
	Ever	1.02 (0.95,1.09)	1.09 (1.06,1.11)
Asian	Never	1.50 (1.34,1.68)	1.37 (1.27,1.47)
	Ever	1.65 (1.55,1.77)	1.56 (1.47,1.65)
Non-Asian	0	1.00	1.00
	1	1.03 (1.00,1.06)	1.06 (1.04,1.07)
	2	1.06 (1.02,1.10)	1.11 (1.08,1.15)
	≥3	1.24 (0.97,1.58)	1.27 (1.11,1.45)
Asian	0	1.47 (1.33,1.64)	1.37 (1.27,1.48)
	1	1.52 (1.40,1.64)	1.47 (1.38,1.56)
	2	1.97 (1.90,2.05)	1.78 (1.68,1.90)
	≥3	2.14 (2.09,2.20)	2.17 (2.09,2.25)

(B)

Race	Stillbirth	Premature menopause RRR (95%CI)	Early menopause RRR (95%CI)
Non-Asian	Never	1.00	1.00
	Ever	1.17 (0.95,1.44)	1.21 (1.19,1.24)
Asian	Never	1.51 (1.36,1.67)	1.38 (1.27,1.50)
	Ever	1.73 (1.62,1.85)	1.57 (1.48,1.67)
Non-Asian	0	1.00	1.00
	1	1.16 (0.91,1.48)	1.18 (1.15,1.20)
	≥2	1.29 (1.21,1.37)	1.55 (1.43,1.68)
Asian	0	1.51 (1.36,1.67)	1.38 (1.28,1.50)
	1 vs 0	1.53 (1.41,1.65)	1.46 (1.38,1.55)
	≥2 vs 0	2.36 (2.25,2.47)	1.90 (1.78,2.04)

(C)

RRR: relative risk ratio. CI: confidence interval. (A) association for infertility, (B) association for miscarriage, (C) association for stillbirth. Models were adjusted for education level, age at menarche, body-mass index, and smoking status. Study variability and within-study correlation were taken into account by including study as a covariate and indicating study as cluster variable in all models.

Figure 1. The association of infertility, miscarriage, and stillbirth with premature or early menopause among Non-Asian and Asian women

(A)

(B)

(C)

RRR: relative risk ratio. CI: confidence interval. (A) association for infertility, (B) association for miscarriage, (C) association for stillbirth. Models were adjusted for education level, age at menarche, body-mass index and smoking status. Study variability and within- study correlation were taken into account by including study as a covariate and indicating study as a cluster variable in all models.