Early menarche, nulliparity and the risk for premature and early natural menopause

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STUDY QUESTION: Are parity and the timing of menarche associated with premature and early natural menopause?

SUMMARY ANSWER: Early menarche (≤ 11 years) is a risk factor for both premature menopause (final menstrual period, FMP <40 years) and early menopause (FMP 40–44 years), a risk that is amplified for nulliparous women.

WHAT IS KNOWN ALREADY: Women with either premature or early menopause face an increased risk of chronic conditions in later life and of early death. Findings from some studies suggest that early menarche and nulliparity are associated with early menopause, however overall the evidence is mixed. Much of the evidence for a direct relationship is hampered by a lack of comparability across studies, failure to adjust for confounding factors and inadequate statistical power.

STUDY DESIGN, SIZE, DURATION: This pooled study comprises 51 450 postmenopausal women from nine observational studies in the UK, Scandinavia, Australia and Japan that contribute to the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE).

PARTICIPANTS/MATERIALS, SETTING, METHODS: Age at menarche (categorized as ≤ 11, 12, 13, 14 and 15 or more years) and parity (categorized as no children, one child and two or more children) were exposures of interest. Age at FMP was confirmed by at least 12 months of cessation of menses where this was not the result of an intervention (such as surgical menopause due to bilateral oophorectomy or hysterectomy) and categorized as premature menopause (FMP before age 40), early menopause (FMP 40–44 years), 45–49 years, 50–51

years, 52–53 years and 54 or more years. We used multivariate multinomial logistic regression models to estimate relative risk ratio (RRR) and 95% CI for associations between menarche, parity and age at FMP adjusting for within-study correlation.

MAIN RESULTS AND THE ROLE OF CHANCE: The median age at FMP was 50 years (interquartile range 48–53 years), with 2% of the women experiencing premature menopause and 7.6% early menopause. Women with early menarche (≤11 years, compared with 12–13 years) were at higher risk of premature menopause (RRR 1.80, 95% CI 1.53–2.12) and early menopause (1.31, 1.19–1.44). Nulliparity was associated with increased risk of premature menopause (2.26, 1.84–2.77) and early menopause (1.32, 1.09–1.59). Women having early menarche and nulliparity were at over 5-fold increased risk of premature menopause (5.64, 4.04–7.87) and 2-fold increased risk of early menopause (2.16, 1.48–3.15) compared with women who had menarche at ≥12 years and two or more children.

LIMITATIONS, REASONS FOR CAUTION: Most of the studies (except the birth cohorts) relied on retrospectively reported age at menarche, which may have led to some degree of recall bias.

WIDER IMPLICATIONS OF THE FINDINGS: Our findings support early monitoring of women with early menarche, especially those who have no children, for preventive health interventions aimed at mitigating the risk of adverse health outcomes associated with early menopause.

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Key words: menarche / parity / premature menopause / early menopause / reproductive health / final menstrual period / InterLACE

Introduction

Women are usually defined as having 'early menopause' if they experience their final menstrual period (FMP) between the ages 40–44 years, which is well before the median age of natural menopause of 51 years for Western countries (North American Menopause Society, 2007). Women diagnosed with 'premature ovarian failure' failure following extended amenorrhoea, hypergonadotropinemia or oestrogen deficiency (Nippita and Baber, 2007) may experience menopause before the age of 40 and are usually classified as having 'premature menopause' (Shuster *et al.*, 2010). These categories for the timing of natural menopause are distinct from when cessation of menses has occurred as a result of medical interventions, such as chemotherapy or bilateral oophorectomy (sometimes referred to as surgical menopause). Women with either premature or early menopause face increased risk of early death and are more likely to suffer from chronic conditions in later life, including cardiovascular disease, Type 2 diabetes and osteoporosis (Gold, 2011; Muka *et al.*, 2016).

Numerous factors influence the timing of the menopause, from genetic and developmental factors to the cumulative effects of hormonal, environmental and lifestyle exposures. For instance, a mother's age at menopause is correlated with her daughter's age at menopause (van Asselt *et al.*, 2004; Forman *et al.*, 2013; He and Murabito, 2014); higher parity is associated with older age at menopause (Gold, 2011); and smoking and teetotalism are established risk factors for younger age at menopause (Gold, 2011; Schoenaker *et al.*, 2014; Taneri *et al.*, 2016). Early menarche is suggested to be associated with the early menopause. However, studies that have examined the links between the timing of menarche and the age at FMP show mixed findings (Hardy and Kuh, 1999; Gold, 2011; Farahmand *et al.*, 2013). Much of the evidence for a direct relationship is hampered by a lack of comparability across studies, including definitional differences of FMP, and lack of adjustment for confounding factors (Gold, 2011; Forman *et al.*, 2013). Lack of statistical power also remains a key issue (Nippita and Baber, 2007).

This study used data from over 50 000 postmenopausal women from populations in the UK, Scandinavia, Australia and Japan to examine associations between the age at menarche and parity with premature menopause and early menopause, while taking into account a range of potential confounding factors. To achieve this objective, we pooled participant-level data from selected studies that contribute to the International collaboration for a Life course Approach to reproductive health and Chronic disease Events (InterLACE) (Mishra *et al.*, 2013, 2016).

Materials and Methods

Ethics

Each study in the InterLACE has been undertaken with ethical approval from the institutional review boards at each participating institution, and all participants provided written informed consent.

Study participants

InterLACE has brought together 20 observational, mostly longitudinal cohort studies with data on women's health. A more detailed description of the InterLACE collaboration has been published previously (Mishra *et al.*, 2013, 2016). Participating studies collected prospective as well as retrospective self-reported survey data on key reproductive, sociodemographic and lifestyle variables. For these analyses, studies were included only if their criteria for sample selection were not based on the menopausal status of the women and data collection included information on the key variables of interest for this analysis, such as age at menarche and age at menopause. The resultant nine studies used for pooling data at the individual level were Australian Longitudinal Study on Women's Health (ALSWH) (Lee *et al.*, 2005), Melbourne Collaborative Cohort Study (MCCS) (Giles and English, 2002), MRC National Survey of Health and Development (NSHD) (Wadsworth *et al.*, 2006), National Child Development Study (NCDS) (Power and Elliott, 2006), English Longitudinal Study of Ageing (ELSA) (Steptoe *et al.*, 2013), UK Women's

Cohort Study (UKWCS) (Cade *et al.*, 2015), Women's Lifestyle and Health Study (WLHS) (Roswall *et al.*, 2015), Danish Nurse Cohort Study (DNCS) (Hundrup *et al.*, 2012) and the Japan Nurses' Health Study (JNHS) (Hayashi *et al.*, 2007). The pooled study sample consisted of 51 450 women who had reported their FMP and had complete information on the covariates used.

Main outcome and exposure variables

Age at FMP was confirmed by at least 12 months of cessation of menses where this was not the result of an intervention (such as surgical menopause due to bilateral oophorectomy or hysterectomy). If the age at FMP was reported multiple times, data reported at the last available survey were used. Using established age at FMP categories for premature and early menopause, the timing of the FMP were classified as premature menopause (before age 40), early menopause (40–44 years), 45–49 years, 50–51 years, 52–53 years and 54 or more years. Age at menarche (categorized as ≤11, 12, 13, 14 and 15 or more years) and parity (categorized as no children, one child and two or more children) were exposure of interest after adjusting for other covariates.

Covariates

The following sociodemographic and lifestyle factors reported at baseline surveys (or at mid age surveys for the birth cohorts) were included in the analysis as covariates: education level (≤10 years, 11–12 years and >12 years), marital status (married or partnered, separated/divorced/widowed and never married/single), smoking status (never smokers, past smokers and current smokers), BMI (<25, 25–30 and ≥30 kg/m^2) and year of birth (born before 1940, between 1940 and 1949 and between 1950 and 1969).

Statistical analysis

Multinomial (polytomous) logistic regression model with five categories of outcome for FMP <40, 40–44, 45–49, 50–51, 52–53 and 54+ years was used to examine the associations between age at menarche and parity with age at FMP adjusted for the covariates mentioned above. Age at FMP of 50–51 was used as a reference category for the outcome, and the regression model was adjusted for birth year, education, smoking status, BMI and marital status as categorical covariates. Categorized variables for age at menarche and parity were first analysed as independent exposure variables and relative risk ratios (RRRs) and 95% CI associated with menarche and parity were estimated separately for each FMP category with age 50–51 as the reference, corresponding to a generalized logit model. Furthermore, to understand whether the joint effect of early menarche and nulliparity on early menopause were simply additive or had a synergistic effect, we included an interaction term between the two exposures in the model and analysed their combined effects. For the combined variable, age at menarche was dichotomized as early (≤11) versus all other (12 or more) and combined with three levels of parity, resulting in six categories in total and the combination of later menarche (menarche age ≥12) and having two or more children was used as a reference category. The higher order categories for age at menarche were collapsed since there were no significant differences in their estimated effects. The SURVEYLOGISTIC procedure (SAS Institute Inc, 2008.) in SAS Version 9.4 was used for the multinomial logistic regression, with the generalized logit link that estimates sampling errors based on the clustered sample survey from multiple studies and incorporates that in the estimates. All tests of statistical hypothesis were done at the two-sided 5% of significance. We also performed study-specific regression and random-effect meta-analysis to estimate the between-study heterogeneity in the effect size estimates.

Results

Study characteristics

There were 51 450 women who have reported their age at FMP and also had complete data on the covariates. Most women were born before 1960, with two-thirds born between 1930 and 1949 (Table I). The mean age at menarche (Table II) was 13.2 years (median 13 years, range 8–20 years), with 14.1% of the women having early menarche (age 11 or less). Three-quarters of the women had two or more children, while 11% had one child and 12% remained nulliparous. Across studies, the prevalence of nulliparity varied from 8.2% (ALSWH) to 20.1% (DNCS). Mean age at FMP (Table III) was 49.9 years (median 50, interquartile range 48–53 years). Overall, 2% of the women experienced premature menopause (ranging across studies from 1% for the DNCS and NSHD to 3.6% for UKWCS), with a further 7.6% having early menopause (ranging from 4.9% for NSHD and JNHS to 9.4% for MCCS). Although women with premature menopause had a mean age at FMP of 36.5 years (SD: 2.5) and median 37.0 (IQR: 35.0, 39.0), two-thirds (68%) had more than one child (results not shown).

Menarche, parity and FMP

Both the timing of menarche and parity were independently associated with age at the FMP and adjusting for confounders or mutual adjustment made no significant difference to their effect estimates. The estimated RRRs for menarche and parity for various age at FMP groups, after mutual adjustment and adjustment for study and confounders (birth year, education level, marital status, smoking status, and BMI) are presented in Table IV. Compared with those who had menarche at age 13 years, women with early menarche had almost twice the relative risk of experiencing premature menopause (RRR 1.80, 95% CI 1.53–2.12) and 31% higher risk of early menopause (RRR 1.31, 1.19–1.44). Similarly, compared with women with two or more children, nulliparous women had over twice the risk of experiencing premature menopause (RRR 2.26, 1.84–2.77), 32% higher risk for experiencing early menopause (RRR 1.32, 1.09–1.59) and 13% higher risk of having menopause at age 45–49 (RRR 1.13, 1.03–1.23).

Combined exposure of early menarche and nulliparity

There was a significant interaction between age at menarche and parity associated with age at the FMP (*P* < 0.0001). The combination of having both early menarche and no children was associated with five times the relative risk of premature menopause (RRR 5.64, 4.04–7.87) and twice the risk of early menopause (RRR 2.16, 1.48–3.15), compared with the reference group (women with menarche at age 12 or later who had two or more children). The increased risks for premature and early menopause were also statistically significant for the combination of having early menarche and only one child (Fig. 1) but to a lesser extent. Meanwhile, nulliparous women with early menarche were also at slightly increased risk of having FMP later than age 51 years.

Meta-analysis

Of the nine studies, six had sufficient data to contribute to the study-specific analysis. Random-effect meta-analysis of the estimates from

Table I Characteristics of individual longitudinal studies of a subset of women past their FMP (with no intervention) in the InterLACE consortium.

Study	Country	N	Age at baseline Mean (Q1, Q3)	Age at last follow-up Mean (Q1, Q3)	Women's year of birth (%)				
					<1930	1930–1939	1940–1949	1950–1959	1960+
Australian Longitudinal Study on Women's Health (ALSWH)	Australia	6327	47.6 (46.4, 48.9)	63.4 (62.6, 65.5)			75.1	24.9	
Melbourne Collaborative Cohort Study (MCCS)	Australia	12 185	58.7 (53.6, 64.6)	67.8 (62.4, 73.6)	35.4	42.4	20.1	2.04	
Danish Nurse Cohort Study (DNCS)	Denmark	8885	59.6 (54.0, 64.0)	69.8 (64.0, 76.0)	29.4	50.8	19.4	0.34	
Women's Lifestyle and Health Study (WLHS)	Sweden/ Norway	5922	44.4 (42.0, 47.0)	55.4 (53.0, 58.0)			72.3	27.7	0.05
MRC National Survey of Health and Development (NSHD)[a]	UK	572	47.0	53.9			100		
National Child Development Study (NCDS)[b]	UK	1907	50.0	54.8				100	
English Longitudinal Study of Ageing (ELSA)	UK	3516	60.0 (52.0, 67.0)	68.6 (61.0, 76.0)	16.0	25.5	35.8	22.4	0.23
UK Women's Cohort Study (UKWCS)	UK	7290	58.1 (52.9, 63.5)	61.0 (55.6, 66.3)	13.1	42.8	39.1	4.84	0.04
Japan Nurses' Health Study (JNHS)[c]	Japan	4846	54.7 (52.0, 57.0)	54.7 (52.0, 57.0)	0.02	1.55	63.6	34.2	0.68
Total		51450	55.0 (48.5, 61.0)	63.4 (56.0, 69.4)	16.4	26.8	40.8	15.9	0.1

FMP, final menstrual period; InterLACE, International collaboration for a Life course Approach to reproductive health and Chronic disease Events.
[a]1946 British birth cohort.
[b]1958 British birth cohort. For birth cohorts studies, data from mid age survey (prior to final menstrual period) have been used as baseline and corresponding ages as baseline age.
Q1—25th percentile, Q3—75th percentile.
[c]Only cross-sectional data were available for analysis for JNHS.

Table II Study-specific and overall reproductive characteristics of subset of women past their FMP (with no intervention) in the InterLACE Consortium.

Study	Age at menarche		Parity distribution		
	Mean (SD)	Median (Q1, Q3)	No children (n = 6199) (%)	One child (n = 5546) (%)	≥2 children (n = 39 705) (%)
ALSWH	12.9 (1.5)	13 (12, 14)	8.2	8.8	83.0
MCCS	13.2 (1.6)	13 (12, 14)	12.7	7.8	79.4
DNCS	13.8 (1.5)	14 (13, 15)	20.1	12.7	67.1
WLHS[a]	13.1 (1.4)	13 (12, 14)	10.0	13.4	76.6
MRC NSHD	12.7 (1.2)	13 (12, 13)	15.4	13.1	71.5
NCDS	12.7 (1.2)	13 (12, 14)	13.0	15.9	71.2
ELSA	13.1 (1.7)	13 (12, 14)	13.4	16.5	70.2
UKWCS	12.9 (1.6)	13 (12, 14)	12.1	11.8	76.0
JNHS	13.1 (1.4)	13 (12, 14)	13.4	10.2	76.4
Overall	13.2 (1.6)	13 (12, 14)	12.0	10.8	77.2

This study included all women who had complete data on education, BMI, smoking and marital status at the baseline.
[a]In WLHS, marital status was only recorded from mothers' birth registry, thus the data were missing for all women who did not give birth. The distribution of parity for WLHS provided in the table is for all women in the study instead of those with complete data on marital status (i.e. the sample used for analysis). Q1—25th percentile, Q3—75th percentile.

the six studies observed a pooled RRR estimate of 4.71 (95% CI 2.81–7.90) for the combined association of early menarche and nulliparity with premature menopause, with no significant heterogeneity between studies (test for heterogeneity P = 0.20, I^2 = 31.9%) in the effect estimate (Fig. 2). The estimated effect size was much larger for JNHS compared with all other studies. When the JNHS was excluded, the combined effect was attenuated slightly to 3.75 (95% CI 2.46–5.72).

Table III Average age at FMP and its categorical distribution by studies in the InterLACE Consortium.

Study	Age at FMP		Categorical distribution of FMP					
	Mean (SD)	Median (Q1, Q3)	<40[a] (n = 1048) (%)	40–44[b] (n = 3927) (%)	45–49 (n = 14 547) (%)	50–51 (n = 12 788) (%)	52–53 (n = 10 152) (%)	54+ (n = 8988) (%)
ALSWH	51.0 (4.3)	51 (49, 54)	1.2	5.8	20.4	23.4	20.1	29.0
MCCS	49.7 (4.5)	50 (47, 53)	2.7	9.4	26.5	24.5	18.6	18.3
DNCS	49.4 (3.7)	50 (47, 52)	1.0	8.2	34.8	25.9	18.4	11.7
WLHS	50.3 (3.7)	51 (48, 53)	1.2	5.1	28.2	24.7	22.0	18.8
MRC NSHD	50.7 (3.3)	51 (49, 53)	1.0	4.9	28.5	28.5	23.8	13.3
NCDS	49.3 (3.8)	50 (48, 52)	2.3	7.6	36.4	18.8	26.1	8.9
ELSA	50.1 (4.9)	50 (48, 53)	3.1	8.6	23.6	25.0	17.0	22.6
UKWCS	49.4 (4.6)	50 (47, 52)	3.6	9.3	27.8	23.5	19.3	16.4
JNHS	49.9 (3.6)	50 (48, 52)	1.2	4.9	31.7	29.9	21.3	11.0
Total	49.9 (4.2)	50 (48, 53)	2.0	7.6	28.3	24.9	19.7	17.5

[a]Premature menopause.
[b]Early menopause, Q1—25th percentile, Q3—75th percentile

Table IV Multivariable adjusted RRR and their two-sided 95% CI of reproductive characteristics and their association with age at FMP using multinomial logistic regression.

Variable	Categories	Age at FMP				
		<40 RRR (95% CI)	40–44 RRR (95% CI)	45–49 RRR (95% CI)	52–53 RRR (95% CI)	54+ RRR (95% CI)
Age at menarche	≤11	1.80 (1.53, 2.12)	1.31 (1.19, 1.44)	1.10 (1.00, 1.21)	1.07 (0.99, 1.15)	1.05 (0.91, 1.21)
	12	1.04 (0.87, 1.25)	1.05 (0.88, 1.26)	0.96 (0.91, 1.02)	0.98 (0.92, 1.05)	0.95 (0.88, 1.02)
	13	Reference	Reference	Reference	Reference	Reference
	14	1.04 (0.79, 1.37)	0.99 (0.90, 1.09)	0.94 (0.86, 1.04)	0.96 (0.90, 1.02)	1.00 (0.95, 1.05)
	≥15	1.10 (0.90, 1.33)	0.98 (0.88, 1.10)	0.94 (0.90, 0.99)	0.91 (0.85, 0.98)	1.09 (1.04, 1.15)
Parity	0	2.26 (1.84, 2.77)	1.32 (1.09, 1.59)	1.13 (1.03, 1.23)	0.92 (0.81, 1.04)	0.89 (0.76, 1.03)
	1	1.53 (1.14, 2.06)	1.23 (1.04, 1.45)	1.12 (1.05, 1.19)	0.94 (0.89, 0.98)	0.90 (0.80, 1.00)
	≥2	Reference	Reference	Reference	Reference	Reference

RRR, relative risk ratio. Reference category for polytomous outcome was the FMP at age 50–51 which was the most common FMP age group. The multivariable model included study, birth year, education, marital status, smoking status, BMI, menarche and parity.

Discussion

To our knowledge, this is the first large-scale multinational study that has found robust evidence for a number of key associations with respect to the timing of the FMP, and particularly for premature and early menopause. In our study, almost 1 in 10 women had premature or early menopause. Having early menarche increased the risk of premature and early menopause by 80%, while the risk doubled for women without children. Furthermore, the combination of early menarche and nulliparity resulted in a 5-fold increased risk of premature menopause and twice the risk of early menopause compared with women having later menarche and two or more children.

Our findings are consistent with previous studies that have established the association between parity and age at natural menopause

(Dorjgochoo et al., 2008; Gold, 2011). Some individual studies included in the InterLACE, such as JNHS (Yasui et al., 2012) and NSHD (Hardy and Kuh, 1999), have also previously shown that nulliparity was associated with early menopause. In contrast with previous reviews that concluded a lack of evidence on the relationship between menarche and menopause (Gold et al., 2001; Gold, 2011; Forman et al., 2013), this study showed associations between early menarche and both early and premature menopause (but no associations were evident for late menarche and the timing of the FMP). Again these findings are consistent with previous results from two individual studies (JNHS (Yasui et al., 2011) and NSHD (Hardy and Kuh, 1999)) that were included in the InterLACE study.

Previous studies have shown that early menarche is associated with poor reproductive functioning, including irregular periods (Hunter,
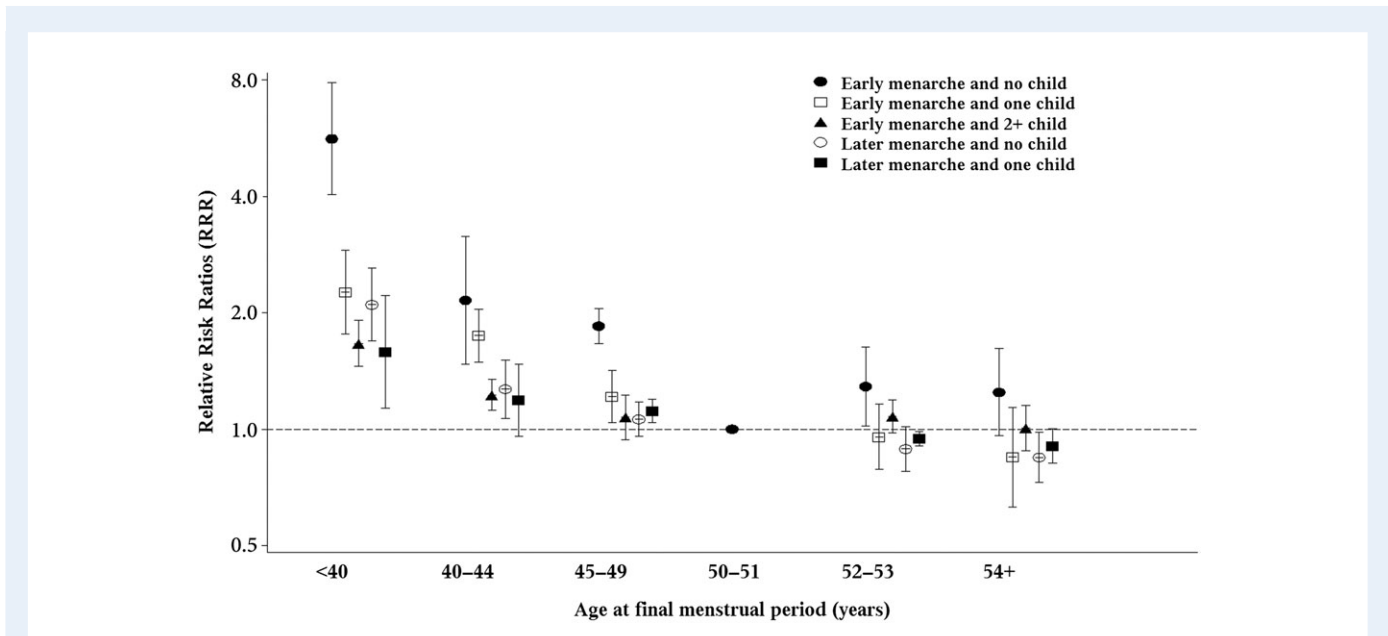
Figure 1 Relative risk ratios (RRRs) and two-sided 95% CI for menopausal age <40, 40–44, 45–49, 52–53 or ≥54 with reference to age 50–51 among women with early (≤11 years) and later age of menarche (12 years or more) in combination with no, one, or two or more children (combination of late age at menarche and two or more children were used as reference group; y-axis on log scale). The estimates were fully adjusted for study cluster, birth year, education, marital status, smoking status and BMI.
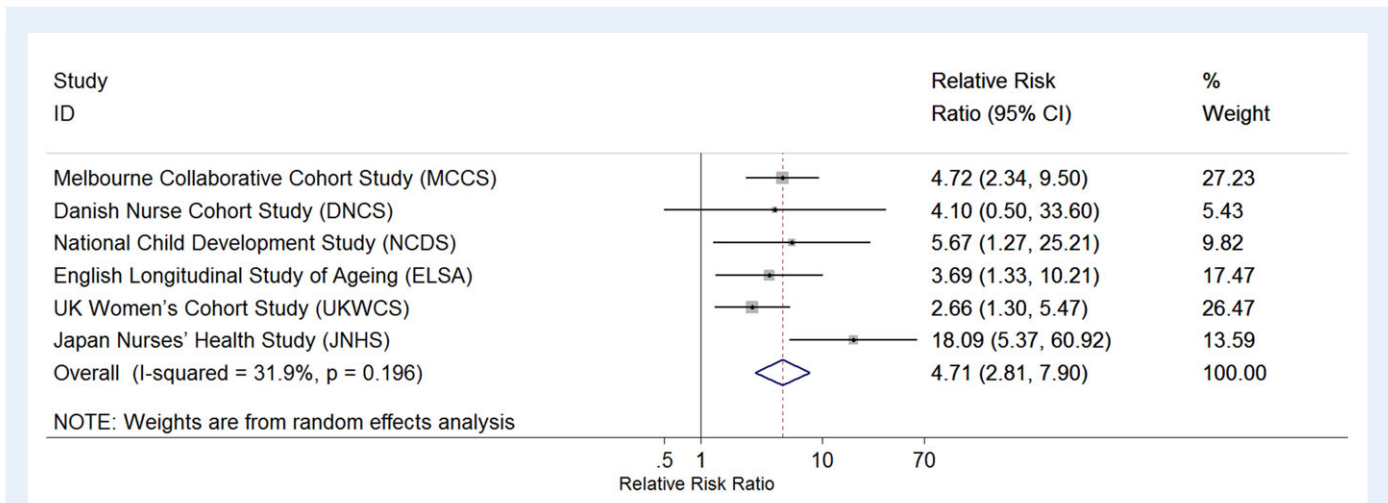
Figure 2 Forest plot of study-specific effect estimates of the association between premature menopause (<40 years) and the combined exposure of early menarche and nulliparity (RRR on log scale). The estimates were fully adjusted for birth year, education, marital status, smoking status and BMI.

1992; Mishra *et al.*, 2009), PCOS (Ibanez *et al.*, 2000) and a slightly increased risk of endometriosis (Nnoaham *et al.*, 2012). Although some women may have used fertility controls to remain childless, parity rates for the generation of women in this study should still reflect fertility, because the childbearing years occurred when general fertility rates were relatively high and prior to the wide availability of advanced treatments for infertility. Further, since the majority of women with premature menopause had their FMP between 35 and 40 years, they had sufficient time to have children, as most did. In this study, 50% of the women had their first child by age 25, 86% by age 30 and 97% by

age 35. It is possible, however, that reproductive decline preceded FMP by 5–10 years and could have impacted fertility. Thus, the greatly increased risk of premature and early menopause among nulliparous women with early menarche is consistent with sub-fertility and accelerated ovarian ageing (Kok *et al.*, 2003). A 'dose response' was also evident: women with early menarche who had one child also faced increased risk of premature and early menopause, but to a lesser extent than nulliparous women. As the timing of menarche is influenced by factors early in life, including by maternal weight gain, childhood obesity and psychosocial stress in childhood (e.g. infant–parent

attachment security), the findings may reflect an underlying common cause for poor reproductive health through the life course (Belsky et al., 2010; Forman et al., 2013). Genetic studies also have shown that a number of menarche-related single-nucleotide polymorphisms (SNPs) collectively predicted age at natural menopause (Day et al., 2015), supporting a causal relationship between the timing of these two reproductive factors. More studies are needed to understand the cumulative and interactive effects of genetic and environmental factors on the association between menarche and menopause.

The main strength of this study was access to individual-level data across several populations across different geographic regions and cultures. The scale of this study was sufficiently large to provide the heterogeneity and statistical power needed to examine premature menopause. The participant-level data in InterLACE enabled harmonization of variables using common definitions, coding and cut points not normally possible with meta-analyses of published results. However, a number of limitations need to be acknowledged. Although InterLACE comprises mainly of longitudinal studies of women in midlife, most of the studies (except the birth cohorts) relied on retrospectively reported age at menarche which may have led to some degree of recall bias. The NSHD has information on age at menarche collected prospectively and retrospectively and found that validity was improved when age categories for menarche were used (as this was the case in this study) (Cooper et al., 2006). Even though 70% of women retrospectively reported their age at menopause at baseline, misclassification was less likely to occur among women with premature or early menopause since women would notice if their menstrual periods stop much earlier than expected. The accuracy of recall could be influenced by educational level and having experienced a stillbirth or miscarriage (Cooper et al., 2006). Women with a history of these pregnancy complications might provide more accurate information as part of understanding their gynaecological history.

Findings in this study of a rather small but statistically significant higher relative risks of later FMP compared with the reference group among nulliparous women with early menarche were unexpected. Study-specific analysis (data not shown) suggested only DNCS contributed to the statistical significance of the finding, with the pooled effect estimate no longer significant when DNCS was excluded. This could be due to some unmeasured confounding associated with that study.

Cohort differences between the women in our study and women who are younger now are unavoidable since our cohorts' members (and any similar study) have to be postmenopausal. In many high-income countries, there has been a long-term decline in the age at menarche, a decline in the mean fertility rate of women, and increased use of fertility treatments (Forman et al., 2013). The robust relationships evident in this study suggest that they are likely to be highly relevant, even if they should be applied with some caution to the current generation of young and mid-aged women.

In summary, this study provides strong evidence for early menarche as a risk factor for both premature and early menopause, a risk that was amplified for nulliparous women. Current guidelines for the clinical management of the menopausal transition, such as those given by National Institute for Health and Care Excellence in the UK, address the diagnosis and treatment options for premature ovarian failure/insufficiency (National Institute for Health and Care Excellence, 2015). It suggests that if the findings of this study were incorporated into clinical guidelines for advising nulliparous women from around the age of 35 years who had an early menarche (≤11 years), clinicians would gain valuable time to prepare these women for the possibility of premature ovarian failure/insufficiency or early menopause. The evidence also strengthens the case for early preventive strategies and clinical surveillance for these women to address the increased risks of chronic diseases associated with earlier menopause.

Authors' roles

G.D.M. conceptualized the study and drafted the manuscript; N.P. performed the statistical analysis and contributed to interpretation of results; H.F.C. performed the literature review and assisted in data management and draft preparation; A.J.D., D.A., D.K., S.S., G.G.G., F.B., K.H., J.S.L., H.M., J.E.C., V.B., D.C.G., A.G., M.K.S., H.O.A., P.D. and E.W. contributed data and provided critical revision of the manuscript for important intellectual content. All authors have read and approved the final version.

Conflict of interest

None declared.

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