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Original article

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The association of birthweight with age at natural menopause: a population study of women in Norway

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Abstract

Background: Previous studies suggest that birthweight may influence age at natural menopause, but the evidence remains inconclusive. Thus, we aimed to estimate the association of birthweight with age at natural menopause.

Methods: A retrospective population study of 164 608 women in Norway, aged 48–71 years. Data were obtained by two self-administered questionnaires among participants in BreastScreen Norway during 2006–2014. We used Cox proportional hazard models to estimate hazard ratios and logistic regression models to estimate odds ratios of menopause according to birthweight. Restricted cubic splines were applied to allow for possible non-linear associations, and adjustments were made for year and country of birth.

Results: Women with birthweight <2500 g were median 51 years at menopause (interquartile range 49–54 years), whereas women with birthweight 3500–3999 g were median 52 years at menopause (interquartile range 49–54 years). The hazard ratio of menopause decreased with increasing birthweight up until 3500 g. At birthweights >3500 g, we estimated no further decrease (P for non-linearity = 0.007). Birthweight at 2500 g increased the odds ratios of menopause before the age of 45 [1.20; 95% confidence interval (CI): 1.14–1.25] and the age of 40 (1.26; 95% CI: 1.15–1.38) compared with birthweight at 3500 g. At birthweights 4000 g and 4500 g, the odds ratio estimates were very similar to the reference group and the CIs overlapped 1.00.

Conclusions: We found a non-linear dose-relationship of birthweight with age at natural menopause, and low birthweight was associated with early natural menopause.

Our findings suggest that growth restriction during fetal life may influence the timing of natural menopause.

Key words: Age at menopause, birthweight, early menopause, growth restriction, population study, primary ovarian insufficiency

Key Messages

- Age at natural menopause increased by increasing birthweight up until 3500 g in a dose dependent manner. At birthweights above 3500 g, there was no further increase in age at menopause.
- Birthweight at 2500 g increased the odds of natural menopause before the age of 45 by 20%, compared to birthweight at 3500 g.
- Our findings suggest that growth restriction during fetal life may influence age at natural menopause.

Introduction

Menopause is the final marker of the end of a woman's reproductive period. Natural menopause occurs between the age of 40 and 60 years in most women.[1] Early menopause (<45 years old) is associated with increased risk of cardiovascular disease and all-cause mortality,[2] and late menopause (≥55 years old) increases the risk of certain hormone-related cancers after menopause.[3] Although genetic factors play a role,[4,5] the mechanisms underlying the timing of menopause are not well understood. Previous studies suggest that factors in very early life may influence age at menopause.[6–15]

A woman is born with a certain number of ovarian follicles, and menopause occurs when the number of ovarian follicles has decreased to a critically low level.[16] It is assumed that no new ovarian follicles are developed after the 20th week of fetal life, and that atresia of the ovarian follicles follows thereafter.[17,18] Thus, the initial number of ovarian follicles and the speed of follicle atresia during fetal life, may be important for a woman's number of ovarian follicles at birth, and thereby the timing of her menopause.

Low birthweight is often used as a proximate measure for adverse environment in fetal life.[19] Low birthweight could therefore be associated with suboptimal fetal development, including suboptimal development of the ovaries. Adverse fetal environment could possibly also increase the rate of follicle atresia during fetal life, and these factors could result in reduced ovarian follicle reserve at birth.[20]

Whether birthweight is associated with age at natural menopause is not known. Three studies, that included <3000 women, reported no association.[6–8] Another study of 22 165 women in the USA, however, suggest that women with birthweight <2500 g may reach natural menopause earlier than women with birthweight 2500–4000 g.[11] Recently, two studies from the UK reported that low birthweight increased the odds of menopause before the age of 45.[12,13] One of these studies suggested that high birthweight also increased the odds.[12]

It remains uncertain whether birthweight is associated with age at menopause. Previous studies have included few women and lacked statistical power to study the association at the borders of the birthweight distribution. No studies yet have studied the shape of the association. Thus, among 164 608 women in Norway born during the years 1936–1966 we aimed to estimate the association of birthweight with age at natural menopause. We also included women who were still having menstrual periods, and we allowed for a possible non-linear relation of birthweight with age at menopause.

Materials and Methods

This study was approved by the Regional Committee for Medical and Health Research Ethics in Norway (reference no. 2014/1711 REK South-East D).

Study design, recruitment and data collection

In this retrospective population-based study, we aimed to include all women with residency in Norway who had participated in BreastScreen Norway during the years 2006–2014.[21] This breast cancer screening programme is administered by the Cancer Registry of Norway (www.kreftregisteret.no) and offers biennial mammographic screening to all women aged 50–69 years old with residency in Norway. During the study period, 84% of all women in Norway partcipated in the

screening programme.[22] Low education and immigrant status is associated with non-participation.[23]

All women who were invited to mammographic screening during the study period were asked to answer two self-administered questionnaires.[24] The questionnaires were enclosed in the postal invitation to the screening and were returned at the examination site. The first questionnaire included questions about sociodemographic factors and birthweight, and the second questionnaire included questions about menstruation, menopausal hormone therapy and surgery on the uterus or the ovaries.

Study sample

Women who answered both questionnaires were eligible for our study. A total of 538 892 women had completed one of the questionnaires. Of these, 400 155 women (74.3%) had answered the first questionnaire and 530 976 women (98.5%) the second. We included the 392 238 (72.8%) women who had completed both questionnaires (Supplementary Figure 1, available as Supplementary data at *IJE* online). We excluded 157 women who reported that menstruation had never occurred, and 35 508 women with missing or implausible information about age at the last menstrual period (<15 or >71 years). We also excluded 1150 women who had undergone surgery with removal of the uterus and/or both ovaries, but did not report age at such surgery. Thereafter, we excluded 190 815 women due to missing or implausible information about birthweight (<500 g or >6500 g) and/or missing information about country of birth. Thus, 164 608 women were included in our data analyses. They were born during the years 1936–1966.

Study factors

Our main exposure variable was birthweight. Information about birthweight was based on the following question: 'What was your weight at birth, in grams?' In the main data analyses, we used birthweight as a continuous variable, and birthweight at 3500 g was the reference. In additional analyses, we grouped birthweight as follows: <2500 g, 2500–2999 g, 3000–3499 g, 3500–3999 g (reference), 4000–4499 g and ≥4500 g.

Our primary outcome was age at natural menopause (in years). Age at menopause was based on the following question: 'Do you still menstruate?' (yes; yes, but irregularly; no). If no, the woman reported her age at the last menstrual period. We performed two secondary analyses. In the first analysis we used natural menopause before the age of 45 (early menopause, yes/no) as the outcome, and in the second analysis we used menopause before the age of 40 (primary ovarian insufficiency, yes/no) as the outcome.

Statistical methods

At the time of data collection, some women had not reached menopause. Therefore, we used survival analyses to estimate median and mean age at natural menopause according to birthweight groups. The associations of birthweight (as a continuous variable) with age at natural menopause were estimated as hazard ratios (HR) by applying Cox proportional hazard models. As follow-up time, we used the number of years from birth until menopause. For women who reported regular (20.8%) or irregular (9.3%) menstrual cycles, follow-up time was until the time of data collection. Women who had undergone hysterectomy (6.2%), bilateral oophorectomy (0.5%) or both of these surgeries (2.8%) prior to natural menopause contributed with follow-up time until time of surgery (censoring). Information about hysterectomy and/or bilateral oophorectomy was obtained by the following questions: 'Have you undergone surgery with removal of the uterus and/or both ovaries?' (no; yes; don't know) and 'If yes, at what age did you undergo such surgery?'. The assumptions for using Cox proportional hazards models were evaluated by Schoenfeld residuals and by inspection of the log–log plots.

Mean birthweight and mean age at natural menopause may have varied during the years 1936–1966[25,26] and may also vary by country of birth.[26,27] Thus, we made adjustment for year of birth (as a continuous variable) and country of birth (coded as Norway, other countries in Europe and countries elsewhere).

We also calculated the proportions of women with natural menopause before the age of 45 and before the age of 40 according to birthweight groups. The associations of birthweight with natural menopause before the age of 45 or before the age of 40 were estimated as odds ratios (OR). All women had reached the age of 45 or 40, but we excluded from these analyses the women who had undergone hysterectomy or bilateral oophorectomy prior to these respective ages.

We allowed for non-linear associations of birthweight with age at natural menopause by applying Cox proportional hazard models and logistic regression models with restricted cubic splines with knots at the 10th, 50th and the 90th percentile of the birthweight distribution (2700 g, 3500 g and 4010 g).[28] Tests for non-linearity were conducted by testing the coefficient of the second spline transformation equal to zero. A 5% significance level was chosen for all analyses. We used the statistical software package Stata/SE version 14.2 (StataCorp, College Station, TX, USA).

To investigate biases due to possible skewed selection to the study sample, we compared the characteristics of

women in our study sample with the characteristics of women who were excluded due to missing or implausible information about birthweight or country of birth. Additionally, we used multiple imputation by chained equations to generate values for birthweight and country of birth.[29] The imputations were based on year of birth, age at data collection, education (coded as ≤11, 12, 13–16 and ≥17 years), smoking habits (coded as never-smoker, former smoker and smoker), menopausal status and age at menopause. We compared the results based on the data with imputed values for birthweight and country of birth with the results from the complete case analyses.

Additionally, we performed supplementary analyses after excluding women who had ever used systemic menopausal hormone therapy or a hormonal intrauterine device, since such use during perimenopause could cause erroneous reporting of menopause. A total of 46.6% (76 660/164 608) were excluded in this analysis. Any current or former use of systemic menopausal hormone therapy (oral or skin patch) was coded as menopausal hormone therapy (yes/no). In our study, older women had failed to report birthweight more often than younger women, and older women may also be more likely to report birthweight erroneously.[30] We therefore performed separate data analyses of women born before 1950 and of women born in 1950 or after.

Results

The mean age of the women was 55.5 years [standard deviation (SD) 5.4 years], and most women (94.2%) were born in Norway (Table 1). Birthweight displayed a normal distribution, but we observed a digit preference for birthweight in whole 1000 g and birthweight ending in 500 g (not shown). Mean birthweight was 3403.7 g (SD 624.1 g). Birthweight was <2500 g for 5.5% of the women, and for 5.2% of the women birthweight was ≥4500 g.

Birthweight and age at natural menopause

The women were median 52 years old at natural menopause [interquartile range (IQR) 49–54 years] (Table 2). Women with birthweight <2500 g were median 51 years old at natural menopause (IQR 49–54 years), whereas women with birthweight 3500–3999 g were median 52 years old (IQR 49–54 years). Figure 1A (based on Cox regression with restricted cubic splines) shows that birthweight was non-linearly associated with age at natural menopause (P for non-linearity = 0.007) (Table 3). The HR of reaching menopause decreased with increasing birthweight up until 3500 g, and the HR for birthweight at 2500 g was 1.05 [95% confidence interval (CI): 1.03–1.06]

Table 1. Characteristics of the study sample ($n = 164\,608$)

	Number	Percent	Mean (SD)
Age at data collection, years			55.5 (5.4)
Undergone natural menopause	99 384	60.4	
Natural menopause before the age of 45[a]	8911	5.7	
Natural menopause before the age of 40[b]	1906	1.2	
Surgery on uterus or ovaries prior to menopause			
Hysterectomy	10 221	6.2	
Bilateral oophorectomy	864	0.5	
Hysterectomy and bilateral oophorectomy	4629	2.8	
Use of systemic menopausal HT	47 293	28.7	
Ever use of hormonal intrauterine device	38 621	23.5	
Birthweight, g			3403.7 (624.1)
Year of birth			
1936–1939	5688	3.5	
1940–1944	17 290	10.5	
1945–1949	28 424	17.3	
1950–1954	37 864	23.0	
1955–1959	46 351	28.2	
1960–1966	28 991	17.6	
Country of birth			
Norway	155 118	94.2	
Europe	7017	4.3	
Other	2473	1.5	

SD, standard deviation; HT, hormone therapy.

[a] $n = 157\,297$ due to exclusion of women with hysterectomy and/or bilateral oophorectomy before the age of 45.

[b] $n = 161\,398$ due to exclusion of women with hysterectomy and/or bilateral oophorectomy before the age of 40.

Table 2. Age at natural menopause and proportions of women with natural menopause before the age of 45 and 40 years according to birthweight groups among women in the BreastScreen Norway, 2006–2014 ($n = 164\,608$)

		Age at menopause (years)[a]				<45 years at menopause[b]			<40 years at menopause[c]		
	Total women	Median	IQR	Mean	95% CI	Total women	No. cases	Percent	Total women	No. cases	Percent
Birthweight, g											
<2500	9071	51	49–54	51.0	50.9–51.1	8587	610	7.1	8833	146	1.7
2500–2999	17 779	52	49–54	51.3	51.2–51.4	16 998	1047	6.2	17 458	220	1.3
3000–3499	55 338	52	49–54	51.3	51.3–51.4	52 951	3020	5.7	54 267	686	1.3
3500–3999	51 181	52	49–54	51.5	51.4–51.5	49 037	2594	5.3	50 264	521	1.0
4000–4499	22 615	52	49–54	51.4	51.3–51.5	21 578	1150	5.3	22 175	241	1.1
≥4500	8624	52	49–54	51.4	51.3–51.5	8137	490	6.0	8401	92	1.1
All women	164 608	52	49–54	51.4	51.3–51.4	157 297	8911	5.7	161 398	1906	1.2

CI, Confidence interval; IQR, interquartile range.

[a]Women with hysterectomy and/or bilateral oophorectomy were censored at the age of surgery ($n = 164\,608$).

[b]Exclusion of women with hysterectomy and/or bilateral oophorectomy before the age of 45 ($n = 7311$).

[c]Exclusion of women with hysterectomy and/or bilateral oophorectomy before the age of 40 ($n = 3210$).

as compared with birthweight at 3500 g (reference). At birthweights >3500 g, we estimated no further decrease in the HR estimates.

Birthweight and natural menopause before the age of 45

In total, 5.7% (8911/157 297) reached natural menopause before the age of 45 (Table 2). The proportion was 7.1% for women with birthweight <2500 g, 5.3% for women with birthweight 3500–3999 g and 6.0% for women with birthweight ≥4500 g. Figure 1B illustrates that birthweight was non-linearly associated with natural menopause before the age of 45 (P for non-linearity < 0.001) (Table 3). The ORs decreased with increasing birthweight up until 3500 g. For women with birthweight at 2500 g, the OR of reaching menopause before the age of 45 was 1.20 (95% CI: 1.14–1.25) compared with birthweight at 3500 g (reference). Above birthweight 3500 g, the ORs of reaching menopause before the age of 45 tended to increase, but the CIs included 1.00.

Birthweight and natural menopause before the age of 40

In total, 1.2% (1906/161 398) of the women reached natural menopause before the age of 40 (Table 2). Among women with birthweight <2500 g, 1.7% reached natural menopause before the age of 40 compared with 1.0% of women with birthweight 3500–3999 g. The ORs of reaching natural menopause before the age of 40 decreased with increasing birthweight up until 3500 g (Figure 1C). For women with birthweight at 2500 g, the OR of reaching menopause was 1.26 (95% CI: 1.15–1.38) compared with birthweight at 3500 g (reference) (Table 3). At birthweights >3500 g, we estimated no further decrease in the OR estimates (P for non-linearity = 0.022).

Supplementary analyses

In separate analyses of women who had never used systemic menopausal hormone therapy or a hormonal intrauterine device, we found similar associations as in the sample as a whole (Supplementary Figures 2A–C, available as Supplementary data at *IJE* online). Likewise, we found similar patterns according to birth cohort (Supplementary Figures 3A and B, available as Supplementary data at *IJE* online). However, the association of birthweight with age at natural menopause was weaker among the women born before 1950 and stronger among the women born in 1950 or after.

The women who had missing or implausible information about birthweight (53.4%) or country of birth (1.5%) were not included in our study sample. The excluded women were older, more often smokers and had lower education than the included women (Supplementary Table 1, available as Supplementary data at *IJE* online). In the analyses of the dataset with imputed values for birthweight and country of birth, we found similar pattern, but weaker associations of birthweight with age at natural menopause than in the complete case analyses (Supplementary Table 2, available as Supplementary data at *IJE* online).

Discussion

In this retrospective population study of 164 608 women in Norway, birthweight was non-linearly associated with age at natural menopause. Age at menopause increased

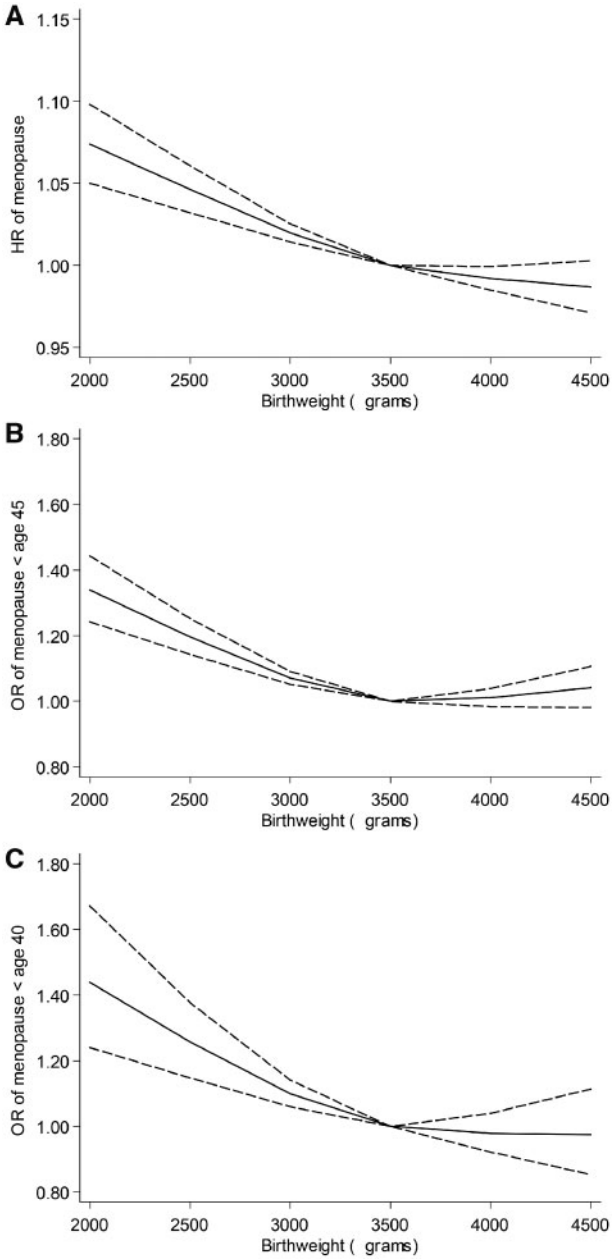

Figure 1. The associations of birthweight with age at natural menopause as estimated by using the Cox proportional hazard model and logistic regression models. Restricted cubic splines were applied to allow for non-linear associations. Birthweight was included as a continuous variable and adjustment was made for year of birth and country of birth. The dashed lines represent 95% confidence intervals. (A) The association of birthweight with age at natural menopause ($n = 164\ 608$). Women with hysterectomy and/or bilateral oophorectomy were censored at the age of surgery. (B) The association of birthweight with natural menopause before the age of 45 ($n = 157\ 297$). Women with hysterectomy and/or bilateral oophorectomy before the age of 45 were excluded. (C) The association of birthweight with natural menopause before the age of 40 ($n = 161\ 398$). Women with hysterectomy and/or bilateral oophorectomy before the age of 40 were excluded.

with increasing birthweight, but at birthweights >3500 g there was no further increase. Compared with birthweight at 3500 g, birthweight at 2500 g was associated with 20% increased odds of menopause before the age of 45 and 26% increased odds of menopause before the age of 40.

We used data from 164 608 women who participated in BreastScreen Norway during the years 2006–2014. This programme offers mammographic screening to all women aged 50–69 years in Norway,[21] but women with low education and immigrants have been less likely to participate.[23] As far as we know, our study is the largest to explore the association of birthweight with age at natural menopause, allowing for non-linear associations. However, the proportion of women who did not report their birthweight was high, as in previous studies.[30] Birthweight was not missing completely at random, since older women, smokers and women with low education were less likely to report birthweight. The associations of birthweight with menopause could therefore be biased due to a skewed selection of women to our study sample. We performed supplementary analyses with imputed values for birthweight, and we found a similar pattern, but weaker association than in the complete case analyses.

The information about birthweight was based on self-report, and birthweights may have been reported inaccurately.[30–32] A meta-analysis of ~80 000 births found high agreement between recalled birthweight and true birthweight.[33] Younger people seem to be more likely than older to report their birthweight accurately.[30,32] It is therefore possible that our estimates for the women who were born in 1950 or after are more reliable than the estimates for the women who were born before 1950.

Also age at menopause may have been erroneously reported.[34,35] For 3.0% of women in our study, the last menstrual period was within the year prior to data collection, and menstrual cycles could possibly reoccur.[36] After exclusion of these women in additional analyses, our results remained virtually unchanged (not shown). Since the occurrence of menopause may be masked for users of systemic menopausal hormone therapy or a hormonal intrauterine device, we performed supplementary analyses without these users. We found, however, very similar results as in the sample as a whole.

Based on a search of the literature and the assumption that birthweight is truly affecting age at menopause, we only made adjustment for possible confounding factors preceding the exposure (birthweight) and being a possible cause of both exposure and outcome (age at menopause). We made adjustment for year of birth and country of birth, but had no information about socio-economic status of the index women's parents. However, the index women's educational level and smoking habits could possibly be used as proxies for parental socio-economic status.[37] Even though such adjustment might imply adjustment for possible mediators, we performed supplementary analyses with

Table 3. Associations of birthweight with age at natural menopause, and with natural menopause before the age of 45 and 40 years among women in the BreastScreen Norway, 2006–2014 ($n = 164\,608$). The associations were estimated as hazard ratios and odds ratios using the Cox proportional hazard model and logistic regression models with restricted cubic splines to allow for non-linear associations; adjustment was made for year of birth and country of birth

	Age at menopause (years)[a]		<45 years at menopause[b]		<40 years at menopause[c]	
	Adjusted HR	95% CI	Adjusted OR	95% CI	Adjusted OR	95% CI
Birthweight, g						
2000	1.07	1.05–1.10	1.34	1.24–1.44	1.44	1.24–1.67
2500	1.05	1.03–1.06	1.20	1.14–1.25	1.26	1.15–1.38
3000	1.02	1.01–1.03	1.07	1.05–1.09	1.10	1.06–1.14
3500	Reference		Reference		Reference	
4000	0.99	0.98–1.00	1.01	0.98–1.04	0.98	0.92–1.04
4500	0.99	0.97–1.00	1.04	0.98–1.11	0.97	0.85–1.11
P for non-linearity	0.007		<0.001		0.022	

CI, Confidence interval; HR, hazard ratio; OR, odds ratio.
[a]Women with hysterectomy and/or bilateral oophorectomy were censored at the age of surgery ($n = 164\,608$).
[b]Exclusion of women with hysterectomy and/or bilateral oophorectomy before the age of 45 ($n = 7311$).
[c]Exclusion of women with hysterectomy and/or bilateral oophorectomy before the age of 40 ($n = 3210$).

adjustment for educational level and smoking habits and found virtually the same results (Supplementary Table 3, available as Supplementary data at *IJE* online). However, other residual confounding may remain.

Four previous studies report no association of birthweight with age at menopause. These studies include a follow-up study of 755 women in the UK,[6] an Australian study of 323 twin pairs[7] and two reports from a prospective study of ~1500 women in the UK.[8,10] Since relatively few women were included, the estimates for age at menopause at the boundaries of the birthweight distribution (for example <2500 g and ≥4000 g) may be uncertain. A recent study of ~100 000 women aged 40–69 years old in the UK, suggested that birthweight is linearly associated with age at menopause.[13] Their data analytic approach, however, did not allow for a possible non-linear association. Also a study of 22 165 women in the USA suggests earlier menopause among women with birthweight <2500 g compared with women with birthweight 2500–4000 g (adjusted HR 1.09; 95% CI: 0.99, 1.20).[11]

A prospective cohort study of 3268 women in the UK found that both birthweight <2500 g and birthweight ≥4000 g increased the odds of menopause before the age of 45 compared with birthweight 3000–3499 g (adjusted OR 1.81; 95% CI 1.02–3.22 and OR 1.84; 95% CI: 1.12–3.03, respectively).[12] In this well-designed study, birthweight was recorded at birth, and the association was stronger than in our study. Another study from the UK reported that the OR of menopause before the age of 45 decreased with increasing birthweight.[13] Their results also suggested an association with menopause before the age of 40, but the CIs included 1.00. Also a case control study of 151 women found no association of birthweight with menopause before the age of 40.[14]

We found that mean age at natural menopause increased with increasing birthweight group up until 3500–3999 g (Table 2). At higher birthweights, we estimated no further increase in age at menopause. Low birthweight is often used as an indicator of growth restriction during fetal life.[19] Impaired growth in fetal life could possibly impair the development of the ovaries and thereby result in early menopause. Growth restriction during fetal life has previously been linked to impaired development of the kidneys, but the effect on ovarian development in humans remains uncertain.[20,38] However, recent animal studies suggest that growth restriction in fetal life has a negative impact on ovarian follicle growth and may accelerate reproductive aging.[39,40]

Women who had their fetal life during the Dutch Hunger Winter in the years 1944–1945 had lower birthweight, and they reached menopause earlier than the women who were not exposed to the famine.[41] This observation suggests that exposures during fetal life may influence age at menopause. Stress and insufficient supply of nutrients during fetal life could possibly also cause changes in gene expressions that persist after birth,[42,43] and thereby increase the risk of early menopause.[44] Women who have been exposed to maternal cigarette smoking[45] or diethylstilbestrol[46] during their fetal life seem to have increased risk of early menopause, although the effect of diethylstilbestrol exposure has been questioned.[11]

We used birthweight as a proximate measure of fetal wellbeing and growth. However, birthweight is also closely related to gestational age at birth. Low birthweight could therefore be an indicator of preterm birth. We lacked

information about gestational age at birth in our study, and we could not separate the effects of low birthweight for gestational age from preterm birth. As for birthweight, preterm birth could also be an indicator of adverse environment in fetal life that possibly could influence ovarian development. For instance, maternal infections, diabetes and preeclampsia are conditions linked to adverse fetal environment and also to preterm birth.[47]

Previous studies of the association of birthweight with age at menopause have been inconclusive.[6–8,10–14] Our findings suggest that women born with low birthweight are at increased risk of early menopause. The results from the sensitivity analyses and the imputed data underlines that the estimated association of birthweight with age at menopause is moderate, but present. Women with birthweight <2500 g had a 7.1% absolute risk of menopause before the age of 45 years, and women with birthweight at 3500–3999 g had a 5.3% absolute risk. Thus, for the individual women born with low birthweight, the absolute increase in risk of early menopause is low and more than 90% of these women will not reach menopause before the age of 45 years. Of all women with menopause before the age of 45 years, only 6.8% had birthweight <2500 g. Thus, few cases with early menopause in our study could be attributed to low birthweight.

In populations where low birthweight is more prevalent than in our study, the prevalence of early menopause may be higher since more women are at risk. Low birthweight[48] and early menopause[1] are more prevalent in developing than in developed countries. Thus, in developing countries, a reduction in the prevalence of low offspring birthweight may also reduce the prevalence of early menopause.

Low birthweight, as well as early menopause, have previously been associated with increased risk of early aging and death.[2,19] Our findings may suggest that the association of low birthweight with early death could be mediated by early menopause. Our findings should therefore encourage further studies about the separate effect and possible joint effects of low birthweight and early menopause on the risk of early aging and death.

Some women face infertility because of early ovarian aging, and ovarian aging has become an important field of research as more women delay childbirth. Thus, our findings also encourage further studies on the impact of the intrauterine environment on ovarian aging and early menopause.

In conclusion, we found that birthweight was non-linearly related to age at natural menopause. Age at natural menopause increased with increasing birthweight up until 3500 g. Above 3500 g, we found no further increase. Our findings suggest that growth restriction during fetal life may influence the timing of natural menopause.

Supplementary data

Supplementary data are available at *IJE* online.

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