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ORIGINAL ARTICLE *Reproductive epidemiology*

The relation of age at menarche with age at natural menopause: a population study of 336 788 women in Norway

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STUDY QUESTION: Is age at menarche associated with age at menopause or with duration of the reproductive period (interval between menarche and menopause)?

SUMMARY ANSWER: The association of age at menarche with age at menopause was weak and non-linear, and the duration of the reproductive period decreased by increasing age at menarche.

WHAT IS KNOWN ALREADY: It remains uncertain whether age at menarche is associated with age at menopause. Some studies report that women with early menarche also have early menopause. Other studies report that women with early menarche have late menopause, or they report no association. The duration of the reproductive period may be an indicator of the cumulative endogenous exposure to estrogens and progestogens during life course and is associated with risk of breast cancer and endometrial cancer.

STUDY DESIGN, SIZE, DURATION: A retrospective cohort study of 336 788 women, aged 48–71 years, in the BreastScreen Norway during the years 2006–2014 was performed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Information about age at menarche and menopausal status was obtained by self-administered questionnaires. We used time to event approaches to estimate the associations.

MAIN RESULTS AND THE ROLE OF CHANCE: Median age at menopause was 51 years in most menarche groups. Women with menarche at age 16 years or age $\geq$ 17 years had menopause 1 year later [median: 52 years, interquartile range (IQR): 49–54 years] than women with menarche at age 13 years (median: 51 years, IQR: 49–54 years, reference) (crude hazard ratio (HR) = 0.95; 95% CI: 0.93–0.97 and 0.95; 95% CI: 0.92–0.99, $P_{non-linearity} < 0.001$). The reproductive period decreased with increasing age at menarche ($P_{non-linearity} < 0.001$), and women with menarche at age $\leq$ 9 years had 9 years longer median reproductive period than women with menarche at age $\geq$ 17 years (median: 43 versus 34 years). Adjustment for year of birth did not change the HR estimates notably.

LARGE SCALE DATA: Not applicable.

LIMITATIONS, REASONS FOR CAUTION: Information about age at menarche and age at menopause was based on self-reports. Particularly for age at menarche, the long time interval between the event and data collection may have caused imprecise reporting.

WIDER IMPLICATIONS OF THE FINDINGS: Our study suggests that age at menarche is a strong indicator for the duration of women's reproductive period. Our findings should encourage studies of the independent role of duration of the reproductive period on the risk of breast cancer and endometrial cancer, since these cancers have been associated with exposure to estrogens and progestogens.

STUDY FUNDING/COMPETING INTEREST(S): The present study was funded by the Norwegian Cancer Society [Grant number 6863294-2015]. The authors declare no conflicts of interest.

Key words: BMI / BreastScreen Norway / menarche / menopause / reproductive period / smoking

Introduction

A woman's age at menopause (last menstrual period) influences her life course fertility, her aging and her risk of early death (Jacobsen et al., 2003; Ossewaarde et al., 2005; Dossus et al., 2010; Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Merritt et al., 2015; Shadyab et al., 2017). Ethnicity (Gold et al., 2001), genetic factors (Perry et al., 2015) and also lifestyle (Dorjgochoo et al., 2008) have been associated with age at menopause. Smoking has consistently been associated with early menopause (Parente et al., 2008; Whitcomb et al., 2017) while high BMI has been associated with late menopause in some studies, but not all (Schoenaker et al., 2014; Szegda et al., 2017). These factors, however, cannot explain the large variation in age at menopause between women.

In addition to age at menopause, also age at menarche (first menstrual period) has been associated with future health (Dossus et al., 2010; Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Charalampopoulos et al., 2014; Day et al., 2015). It remains uncertain, however, whether age at menarche is related to age at menopause (Forman et al., 2013). Some studies report that women with early menarche also have early menopause (Hardy and Kuh, 1999; Nagata et al., 2000; Henderson et al., 2008; Brand et al., 2015; Li et al., 2016; Mishra et al., 2017; Ruth et al., 2016). Other studies report that women with early menarche have late menopause (van Keep et al., 1979; Boulet et al., 1994), or they report no association (van Noord et al., 1997; Kato et al., 1998; Nagel et al., 2005; Dratva et al., 2009; Otero et al., 2010; Bjelland et al., 2014; Rizvanovic et al., 2013; Yasui et al., 2012; Zsakai et al., 2015). If age at menarche is not related to age at menopause, women with early menarche may have a longer time interval between menarche and menopause than women with late menarche. This interval is often referred to as the woman's reproductive period.

A long reproductive period implies high cumulative exposure to endogenous female sex hormones such as estrogens and progestogens, and has consistently been associated with increased risk of hormone related cancers, such as breast cancer and endometrial cancer (Dossus et al., 2010; Wu et al., 2014). In contrast, a long reproductive period has also been associated with a reduced risk of cardiovascular disease (Mansoor et al., 2017), but the associations with all-cause mortality have been inconsistent (Jaspers et al. 2017; Shadyab et al., 2017). The duration of the reproductive period is closely linked to age at menarche and age at menopause. To better understand the independent role of the reproductive period on disease risk, reliable knowledge about the relation of age at menarche with age at menopause and with duration of the reproductive period is important.

Among 336 788 women participating in the BreastScreen Norway, we aimed to estimate age at natural menopause according to age at menarche. We also estimated the time interval from menarche to natural menopause (reproductive period) according to age at menarche.

Materials and Methods

Study design, recruitment and questionnaires

The BreastScreen Norway is administered by the Cancer Registry of Norway (www.kreftregisteret.no), and mammographic examination is offered biannually to all women at age 50–69 years (Hofvind, 2015). The overall participation rate in the screening program is 75%, and women older than 60 years are more likely to participate than younger women. All women who attended the screening program during the years 2006–2014 were invited to answer a questionnaire about their health and lifestyle prior to age 50 years and also a questionnaire about current health and lifestyle (Hofvind, 2015). The questionnaires were attached to the postal invitation to the first screening examination, and were returned at the examination site. In total, 538 892 women answered at least one of the questionnaires. Of these, 25.7% did not answer the first questionnaire whereas 1.5% did not answer the second.

The 392 238 women who had completed both questionnaires were included in our study (Fig. 1). We excluded 157 women who reported that menstruation had never occurred. Thereafter, we excluded 35 508 women who had not answered the questions about the last menstrual period, or who had outlying values for age at last menstrual period (<15 and >71 years). We also excluded 1150 women who had undergone hysterectomy and/or bilateral oophorectomy, but did not report age at such surgery. Finally, we excluded 18 635 women who did not report age at menarche, or who had outlying values for age at menarche (<5 and >25 years), leaving 336 788 women to our study sample. The women were born during the years 1936–1967.

Study factors

Age at menarche (in years) was based on the following question: 'At what age (years old) did you have your first menstrual period?' In the data analyses, age at menarche was categorized as ≤9, 10, 11, 12, 13, 14, 15, 16 and ≥ 17 years, and we used women with menarche at age 13 as the reference group.

Age at menopause (in years) was based on the following two questions: 'Are you still having menstrual periods?' (yes; yes, but irregularly; no), and 'If you no longer have menstrual periods, how old were you at your last menstrual period?'

We use the term 'reproductive period' for the time interval from menarche to menopause (in number of years).

Statistical analyses

Not all women had undergone menopause at the time of screening. In total, 16.9% of the women reported regular, and 7.9% reported irregular, menstrual cycles. To avoid underestimation of age at menopause, we used the Kaplan–Meier method to estimate median age at menopause with interquartile ranges (IQR) and mean age at menopause with 95% CI. We also used the Kaplan–Meier method to estimate the probability (at any time after birth) of having undergone menopause. As follow-up time, we used the number of years from birth until menopause. For women who were still having menstrual cycles, follow-up time was until the end of data collection (screening examination) (Cologne et al., 2012). Women who had undergone hysterectomy (6.2%), bilateral oophorectomy (0.6%) or both surgeries (3.0%) before natural menopause, contributed with follow-up time until the time of surgery.

We estimated the associations of age at menarche with menopause as crude hazard ratios (HR) with 95% CI by applying Cox proportional hazard models. Adjustment was made for year of birth. HR > 1.00 indicate earlier menopause compared to the reference group (menarche at age 13 years), whereas HR < 1.00 indicate later menopause. The proportional hazards assumption was evaluated by Schoenfeld residuals, and by inspection of log-log plots. We tested for trends by applying Cox proportional hazard models with restricted cubic splines with knots at the 10th, 50th and 90th percentiles of the distribution (menarche at age 11, 13 and 15 years) (Orsini and Greenland, 2011). 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.
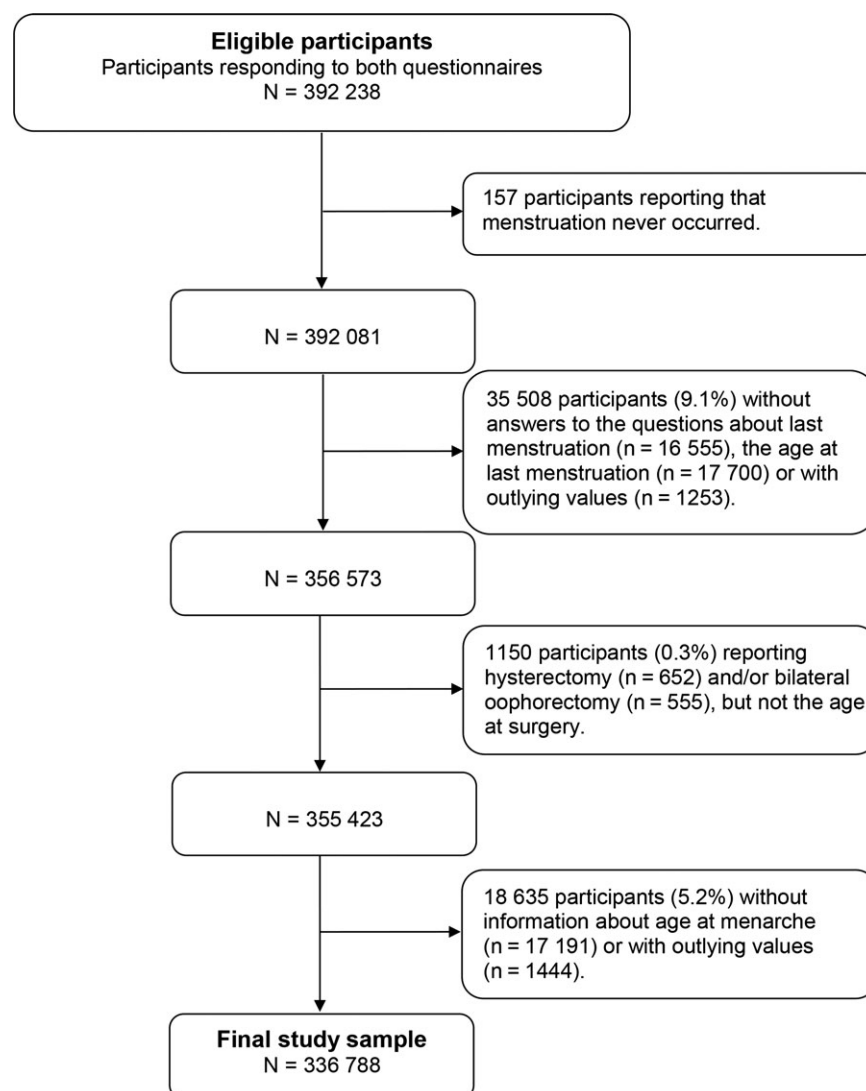
Figure 1 Flow chart of the study sample; 336 788 women in the BreastScreen Norway, 2006–2014.

We used similar methods to assess the association of age at menarche with the duration of the reproductive period (in years). In these analyses, we used time from menarche until menopause, censoring or end of data collection (as defined above) as follow-up time. HR > 1.00 indicate shorter reproductive period compared to the reference group (menarche at age 13), whereas HR < 1.00 indicate longer reproductive period.

We performed sensitivity analyses of the association of age at menarche with age at menopause among women who had never used systemic menopausal hormone therapy or a hormonal intrauterine device. Current or former use of systemic menopausal hormone therapy (oral or skin patch) was defined as menopausal hormone therapy use (yes/no). To further explore the role of smoking habits (Parente et al., 2008; Whitcomb et al., 2017) and BMI (Schoenaker et al., 2014; Szegda et al., 2017) on age at menopause, we also repeated the data analyses within subgroups of women according to smoking habits (nonsmoker and current smoker) and BMI status (BMI < $25 \, kg/m^2$ and BMI ≥ $25 \, kg/m^2$). BMI at the time of the screening examination was calculated as weight (kg) divided by square height (m^2). Smokers were women who reported any smoking at the time of the data collection.

All data analyses were performed by using Stata/SE version 14.2 (StataCorp, College Station, TX, USA).

Ethical approval

This study was approved by the Regional Committee for Medical and Health Research Ethics in Norway [reference no. 2014/1711 REK South-East D]. All women received written information about the study together with the invitation to participate. By returning the questionnaires, the woman agreed to participate.

Results

Mean age at screening was 56.7 years (SD 5.8 years, range: 48–71 years), and the vast majority (92.9%) were born in Norway (Table I). Mean BMI of the women was $25.8 \, kg/m^2$ (SD $4.6 \, kg/m^2$), and 26.0% were smokers. Median age at menarche was 13 years [IQR: 12–14 years, mean 13.3 years (SD 1.4 years)].

Table I Characteristics of the study sample; 336 788 women in the BreastScreen Norway, 2006–2014.

	Number	Percentage (%)	Mean	SD
Undergone natural menopause	220 779	65.6		
Surgery on uterus and ovaries prior to menopause				
Hysterectomy	20 976	6.2		
Bilateral oophorectomy	1945	0.6		
Hysterectomy and bilateral oophorectomy	9995	3.0		
Ever use of systemic menopausal hormone therapy	101 627	30.2		
Ever use of hormonal intrauterine device	69 882	20.8		
Current smoker	87 537	26.0		
BMI, kg/m^{2a}			25.8	4.6
Age at data collection, years			56.7	5.8
Age at menarche, years			13.3	1.4
Place of birth				
Norway	313 006	92.9		
Europe	13 710	4.1		
North America	1521	0.5		
South America	970	0.3		
Asia	4729	1.4		
Africa	661	0.2		
Oceania/Australia	109	0.0		
Missing information	*2082*			
Year of birth				
<1940	18 280	5.4		
1940–1944	48 301	14.3		
1945–1949	67 249	20.0		
1950–1954	75 612	22.5		
1955–1959	79 681	23.7		
≥1960	47 665	14.2		

[a]$N = 308\,532.$

Age at menarche and age at menopause

Overall, median age at menopause was 51 years [IQR: 49–54 years, mean 51.11 years (95% CI: 51.09–51.13 years)] (Table II). The association of age at menarche with age at menopause was non-linear ($P_{non\text{-}linearity} < 0.001$). Women with menarche at age 16 or age ≥17 years had menopause 1 year later than the reference group (menarche at age 13 years) [median: 52 years (IQR: 49–54 years) versus median 51 years (IQR: 49–54 years)]. Thus, women with menarche at age 16 or ≥17 years had the lowest hazard rates of menopause (crude HR = 0.95; 95% CI: 0.93–0.97 and crude HR = 0.95; 95% CI: 0.92–0.99) (Table II). The point estimated HR for the menarche groups age 15 years or earlier was close to 1.00, and thus, non-different from women with menarche at age 13 years (reference). Adjustment for the woman's year of birth did not change the estimates notably. The absolute difference in mean age at menopause between any menarche group did not exceed 1 year [minimum mean 50.92 years (95% CI: 50.47–51.37 years) versus maximum mean 51.29 years (95% CI: 51.20–51.37 years)] (Table II). Figure 2 illustrates the probability of menopause at any time after birth for each menarche group.

Among nonusers of menopausal hormone therapy or a hormonal intrauterine device (46.8% of total), we observed a similar non-linear association of age at menarche with age at menopause as for the sample as a whole (Supplementary Table SI). Overall, smokers were 2 years younger at menopause than nonsmokers [median: 50 years (IQR: 48–53 years) versus 52 years (IQR: 49–54 years)], and women with BMI < 25 kg/m^2 were 1 year younger at menopause than women with BMI ≥ 25 kg/m^2 [median 51 years (IQR: 49–54 years) versus 52 years (IQR: 49–54 years)]. We observed the same dose response pattern among nonsmokers, women with BMI < 25 kg/m^2 and among women with BMI > 25 kg/m^2 as in the sample as a whole (Supplementary Tables SII and SIII). Among smokers, no such dose response pattern was observed. Within all subgroups above, however, we estimated less than 1 year difference in mean age at menopause between menarche groups.

Age at menarche and duration of the reproductive period

Median duration of the reproductive period was 38 years (IQR: 35–41 years), and mean duration was 37.95 years (95% CI: 37.93–37.97

Table II Associations of age at menarche with age at menopause among 336 788 women in the BreastScreen Norway, 2006–2014.

	No. women	Age at menopause (years)				Crude HR[a]	95% CI	Adjusted HR[b]	95% CI
		Mean	95% CI	Median	IQR				
Age at menarche									
≤ 9 years	959	50.92	50.47–51.37	51	48–54	1.02	0.94–1.11	1.05	0.96–1.14
10 years	5359	50.93	50.75–51.10	51	48–54	1.01	0.97–1.04	1.02	0.99–1.06
11 years	27 952	51.07	51.01–51.14	51	49–54	0.99	0.98–1.01	1.00	0.98–1.02
12 years	66 045	51.14	51.10–51.18	52	49–54	0.99	0.98–1.00	0.99	0.98–1.00
13 years	93 013	51.11	51.08–51.14	51	49–54	Reference		Reference	
14 years	81 863	51.05	51.01–51.09	51	49–54	1.02	1.01–1.03	1.01	1.00–1.02
15 years	43 659	51.16	51.11–51.21	51	49–54	0.99	0.97–1.00	0.98	0.97–0.99
16 years	13 610	51.29	51.20–51.37	52	49–54	0.95	0.93–0.97	0.94	0.92–0.96
≥17 years	4328	51.17	51.00–51.35	52	49–54	0.95	0.92–0.99	0.96	0.92–0.99
Total	336 788	51.11	51.09–51.13	51	49–54				
$P_{non-linearity}$[c]							<0.001		<0.001

[a]Associations of age at menarche with menopause are estimated as crude hazards ratios (HR) with 95% CI by applying Cox proportional hazard models. HR > 1.00 indicates earlier menopause and HR < 1.00 indicates later menopause compared to the reference group (menarche at age 13 years).
[b]Adjusted for year of birth.
[c]Tests for trend were conducted by using Cox proportional hazard models with restricted cubic splines with three knots at fixed percentiles of the distribution (menarche at age 11, 13 and 15 years). Tests for non-linearity were conducted by testing the coefficient of the second spline transformation equal to zero.
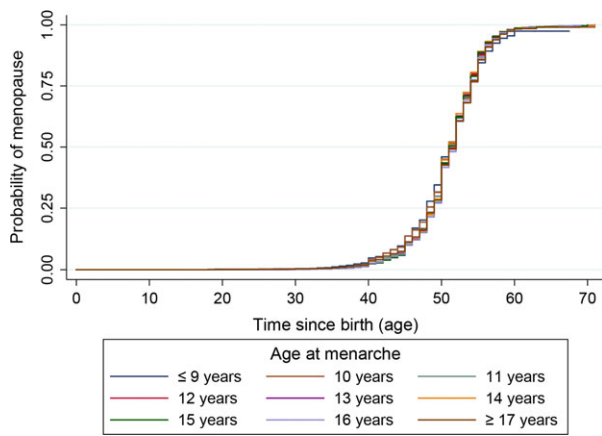IQR, interquartile range.

Figure 2 Probability of menopause according to age at menarche as estimated by the Kaplan–Meier method; follow-up time since birth.

years). For each 1-year increase in age at menarche, the median duration of the reproductive period decreased by ~1 year (Table III). Thus, the later menarche occurred, the shorter was the median reproductive period. Among women with menarche at age 9 years or earlier, the reproductive period was at least 9 years longer than among women with menarche at age 17 years or later (median: 43 versus 34 years). Accordingly, the HR for menopause (from menarche) increased with increasing age at menarche. Figure 3 illustrates the probability of menopause at any time after menarche for each menarche group.

Discussion

In this retrospective cohort study of 336 788 women in Norway, the median age at menopause was 51 years, and age at menopause was almost independent of age at menarche. Accordingly, women with early menarche had, on average, several years longer interval from menarche to menopause (reproductive period) than women with late menarche.

Our study is the largest yet to explore the association of age at menarche with age at menopause. Thus, we had statistical power to estimate age at menopause for women with very early or very late menarche, and also to study the shape of the associations. We used data from the BreastScreen Norway during the years 2006–2014. This program aims to include all women at age 50–69 years who live in Norway, and ~75% of all eligible women participate. Approximately 64%, of all participants answered the questionnaires that we used in our study (Hofvind, 2015). Women who did not answer the questions about age at menarche or menopause, or who had outlying values, were not included in the data analyses. However, age at menarche and age at menopause in our study were very similar to other reports from Norway (Bjelland et al., 2014), suggesting that the women included are representative for all women in Norway. It is therefore unlikely that a possible skewed selection to our study will have biased the estimated association of age at menarche with age at menopause.

Information about age at menarche and age at menopause (in whole years) was obtained by self-reports in questionnaires. Particularly, age at menarche may have been erroneously reported by some women since the time interval from the event to data collection was long. Yet, menarche is an important event in a woman's reproductive life, and previous studies have found that recalled and actual ages at menarche

Table III Associations of age at menarche with duration of the reproductive period among 336 788 women in the BreastScreen Norway, 2006–2014

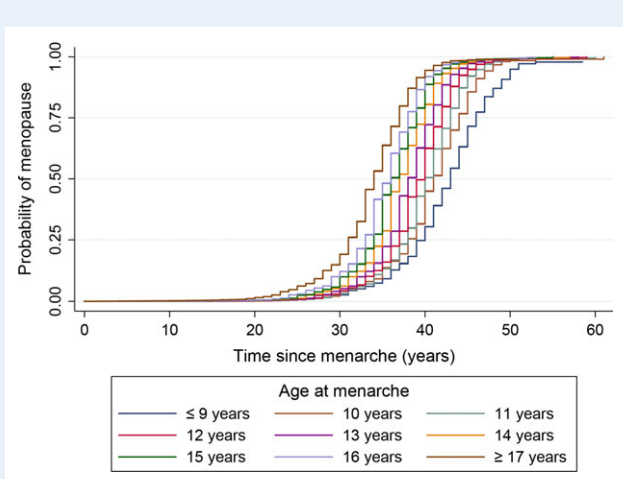| | No. women | Duration of the reproductive period (years)[a] | | | | | | | |
		Mean	95% CI	Median	IQR	Crude HR[b]	95% CI	Adjusted HR[c]	95% CI
Age at menarche									
≤ 9 years	959	42.61	42.16–43.05	43	40–46	0.38	0.35–0.41	0.41	0.38–0.44
10 years	5359	40.93	40.75–41.10	41	38–44	0.52	0.50–0.53	0.54	0.53–0.56
11 years	27 952	40.07	40.01–40.14	40	38–43	0.62	0.62–0.63	0.64	0.63–0.65
12 years	66 045	39.14	39.10–39.18	40	37–42	0.77	0.77–0.78	0.78	0.78–0.79
13 years	93 013	38.11	38.08–38.14	38	36–41	Reference		Reference	
14 years	81 863	37.05	37.01–37.09	37	35–40	1.32	1.30–1.33	1.29	1.28–1.31
15 years	43 659	36.16	36.11–36.21	36	34–39	1.67	1.65–1.70	1.63	1.60–1.65
16 years	13 610	35.29	35.20–35.38	36	33–38	2.08	2.03–2.13	2.00	1.95–2.05
≥17 years	4328	33.78	33.60–33.95	34	31–37	3.07	2.92–3.23	2.97	2.82–3.13
Total	336 788	37.95	37.93–37.97	38	35–41				
$P_{non-linearity}$[d]							<0.001		<0.001

[a]Duration of the reproductive period is defined as the number of years between menarche and menopause.
[b]Associations of age at menarche with number of reproductive years are estimated as crude hazards ratios (HR) with 95% CI by applying Cox proportional hazard models. HR > 1.00 indicates shorter time from menarche to menopause and shorter reproductive period compared to the reference group (menarche at age 13 years). HR < 1.00 indicates longer time from menarche to menopause and longer reproductive period.
[c]Adjusted for year of birth.
[d]Tests for trend were conducted by using Cox proportional hazard models with restricted cubic splines with three knots at fixed percentiles of the distribution (menarche at age 11, 13 and 15 years). Tests for non-linearity were conducted by testing the coefficient of the second spline transformation equal to zero.
IQR, interquartile range.

Figure 3 Probability of menopause according to age at menarche as estimated by the Kaplan–Meier method; follow-up time since menarche.

are moderately to highly correlated (Must *et al.*, 2002; Cooper *et al.*, 2006). Similar results have been reported for age at menopause (Rodstrom *et al.*, 2005). Age at menopause is typically defined retrospectively as 12 months without menstrual periods (Soules *et al.*, 2001). In our study, time since the last menstrual period was not reported. In accordance with a previous study (Hahn *et al.*, 1997), we observed digit preference for menopause ages ending with 0, 2 and 5, suggesting imprecise reporting of exact age at menopause in some

women (data not shown). Also errors in reporting of surgery on the uterus and ovaries may have occurred (Phipps and Buist, 2009). Imprecise reporting of menopause may have deflated our estimated associations, but we have no reason to believe that possible erroneous reporting of age at menopause was differential by age at menarche.

Based on a literature review of factors associated with age at menarche and menopause, and the assumption that age at menarche is truly related to age at menopause, we evaluated possible confounding factors of the associations using directed acyclic graphs (Pearl, 1993). A confounding factor is a common cause of both the exposure (menarche) and the outcome (menopause). Smoking and adult BMI have been associated with age at menopause (Parente *et al.*, 2008; Schoenaker *et al.*, 2014). We have little reason to assume that women were smokers or had high BMI before puberty, and therefore, we did not consider these factors as possible confounders. If age at menopause truly is independent of age at menarche, such a finding is expected to be consistent within different groups of women. Thus, we repeated our main analyses within subgroups of women according to their current smoking status and BMI. We found similar associations in subgroups as for the sample as whole.

Most prior studies of the association of age at menarche with age at menopause have included relatively few women (van Keep *et al.*, 1979; Boulet *et al.*, 1994; Kato *et al.*, 1998; Hardy and Kuh, 1999; Nagata *et al.*, 2000; Nagel *et al.*, 2005; Dratva *et al.*, 2009; Otero *et al.*, 2010; Rizvanovic *et al.*, 2013; van Noord *et al.*, 1997). Therefore, they lacked statistical power to study separately women at the boundaries of the age at menarche distribution (e.g. ≤9 and ≥17 years). In our study, the high statistical power could lead to misinterpretations of the findings; small statistically significant differences could be erroneously interpreted as clinically important differences.

Also, many prior studies have estimated the association of age at menarche with menopause without applying a time to event approach (van Keep et al., 1979; Boulet et al., 1994; van Noord et al., 1997). Thus, their reported age at menopause may represent underestimates, and the relationship of age at menarche with age at menopause may possibly be biased. By using a time to event approach, women who had undergone surgical removal of the uterus and/or both ovaries prior to menopause contributed with follow-up time until the time of surgery. Likewise, women who were still having menstrual periods contributed with follow-up time until the time of data collection. In some previous studies that have applied a time to event approach, women who had undergone surgical removal of the uterus and/or both ovaries prior to menopause were excluded (Kato et al., 1998; Nagel et al., 2005; Zsakai et al., 2015). Such exclusion may have introduced sources of bias, since healthy women have been overrepresented. However, the most recent studies of the association of age at menarche with age at menopause have censored women at the attained age at surgery (Henderson et al., 2008; Otero et al., 2010; Yasui et al., 2012; Brand et al., 2015; Li et al., 2016; Ruth et al., 2016).

Some women start using systemic hormone therapy prior to menopause and may therefore have vaginal bleedings that mask the occurrence of natural menopause. The statistical handling of women who use systemic hormone therapy prior to menopause differs between studies (Gold, 2011), or is not described (Otero et al., 2010; Yasui et al., 2012; Zsakai et al., 2015). As in recent studies (Dratva et al., 2009; Brand et al., 2015; Li et al., 2016), we report results also after exclusion of women who reported use of systemic hormone therapy and/or a hormonal intrauterine device, and we found virtually the same associations as in the sample as a whole. In additional data analyses, we censored women at age of startup of systemic hormone therapy, as suggested in some studies (Henderson et al., 2008; Gold, 2011; Ruth et al., 2016). By applying such an approach, our estimated associations did not change notably (data not shown). We lacked information about age at startup of systemic hormone therapy for 16.6% of the women with natural menopause.

Also use of oral contraceptives can mask the occurrence of natural menopause. Unfortunately, age at cessation of oral contraceptive use was not reported. Use of oral contraceptives has been discouraged after age 40 years until in recent years (ESHRE Capri Workshop Group, 2009). It is therefore unlikely that oral contraceptives use has masked natural menopause for a large proportion of women in our study.

Some studies that have aimed to identify determinants of age at menopause included many factors in addition to age at menarche in multivariable data analyses, such as smoking, adult BMI and parity (Henderson et al., 2008; Ruth et al., 2016). These factors may mediate the association of age at menarche with age at menopause, and adjustment for mediating factors may introduce biases in the estimates (Schisterman et al., 2009). Our results confirm results from previous studies that current smokers reach menopause 1–2 years earlier than nonsmokers (Parente et al., 2008), and also that women with a low BMI reach menopause earlier than women with high BMI (Schoenaker et al., 2014).

Many prior studies that have used time to event analysis in their data analytic approach (Kato et al., 1998; Nagel et al., 2005; Dratva et al., 2009; Bjelland et al., 2014; Otero et al., 2010; Yasui et al., 2012; Zsakai et al., 2015) report no association of age at menarche with age at menopause. To our knowledge, no such studies have reported that

age at menopause decreases with increasing age at menarche. The largest study yet, including 100 707 women in the UK during the years 2006–2010, reported that age at menopause increases linearly with increasing age at menarche (Ruth et al., 2016). The Ruth et al. (2016) study, and other studies that report a positive association, suggest small absolute differences in age at menopause between menarche groups (Henderson et al., 2008; Brand et al., 2015; Li et al., 2016).

Unlike previous studies, we allowed for a non-linear association of age at menarche with age at menopause in our data analytic approach. We found that the HR of menopause was almost identical in all menarche groups at age 15 years or earlier, and that women with menarche at age 16 or 17 years or later had a lower HR of menopause, as compared to the other menarche groups. Thus, age at menarche was non-linearly associated with age at menopause. We did not observe such a dose response relation among smokers, but the statistical power in the boundaries of age at menarche was rather low in this subgroup and type two errors may have occurred.

We are aware of no studies that have estimated the duration of the reproductive period according to age at menarche by using a time to event approach. Nevertheless, our results are similar to a Chinese cohort study of 33 054 postmenopausal women, aged 40–70 years (Dorjgochoo et al., 2008). By using a linear regression model, they estimated that women with menarche at age 11 years or earlier had at least 5.4 years (95% CI: 4.9–5.9) longer reproductive period than women with menarche at age 16 years or later. Overall, their reported duration of the reproductive period was almost 4 years shorter than in our study. However, they included only women who had undergone menopause in the data analyses (49.6% of the cohort). Their study sample may therefore represent a selection of women with early menopause, and the duration of the reproductive period may be underestimated.

We found that age at menopause was close to 51 years, and almost independent of age at menarche. Our findings therefore suggest that the onset of menarche and the onset of menopause are regulated by different biological mechanisms (Apter and Hermanson, 2002; Broekmans et al., 2009). The number of ovarian follicles reaches its maximum during fetal life, and atresia of the ovarian follicles starts before a woman is born (Baker, 1963). It is assumed that menopause occurs when the number of ovarian follicles has declined to below 1000 (Richardson and Nelson, 1990; Faddy and Gosden, 1996). Our results do not suggest that the number of menstrual cycles during life course is important for the timing of menopause, although each menstrual cycle recruits several ovarian follicles that degenerate. The rate of follicle atresia, independent of the number of menstrual cycles, may be more important (Ginsberg, 1991).

Age at menopause was almost independent of age at menarche. However, women who were 16 or ≥17 years at menarche (5.3%) reached menopause slightly later than the reference group (13 years at menarche). Although age at menarche shows great inter-individual variation, menarche occurs between age 10 and 16 years in most girls (Rees, 2006). Women who were 16 or ≥17 years at menarche could represent girls with low BMI and/or high levels of exercise, since these factors may delay menarche (Rees, 1993). It is possible that lean girls who exercise at high levels adapt a lifestyle in adult life which could delay menopause (Schoenaker et al., 2014).

We report that for each year of delay in menarche, the reproductive period decreased by ~1 year. Hence, our findings suggest that women

with early menarche have a longer reproductive period and higher cumulative exposure to endogenous sex hormones, such as estrogens and progestogens, than women with late menarche. The increased risk of breast cancer in women with early menarche (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Wu *et al.*, 2014) could therefore possibly be explained by the longer reproductive period in these women. The independent effect of early menarche and of the duration of the reproductive period on breast cancer risk is being debated (Collaborative Group on Hormonal Factors in Breast Cancer, 2012).

Also, endometrial cancer (Dossus *et al.*, 2010) and cardiovascular disease (Day *et al.*, 2015) have been linked to early menarche. Whether age at menarche is an independent risk factor for these diseases, or a proximate measure for the duration of the reproductive period, is to our knowledge not known. Thus, our findings should encourage studies of the independent role of age at menarche, age at menopause and duration of the reproductive period on the development of disease in women.

In this large population study of 336 788 women in Norway, median age at menopause was close to 51 years, and age at menopause was almost independent of age at menarche. Accordingly, women with early menarche had, on average, a reproductive period that was several years longer than women with late menarche.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Authors' roles

E.K.B. and A.E. had the original idea for this study. E.K.B. performed the analyses, made the tables and figures, and wrote the major part of the article. A.E. contributed with writing of the article, interpretation of the results, and was the guarantor of the study. S.H. had a significant role in the data collection. L.B. contributed with interpretation of the results. S.H. and L.B. discussed the design, critically revised the article, and agreed on the final version. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analyses. All authors have approved the submitted version of the article.

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Conflict of interest

None to declare.

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