Original Contribution

Association of Low Age at Menarche with Increased All-Cause Mortality: A 37-Year Follow-up of 61,319 Norwegian Women

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Little is known about the impact of age at menarche on later mortality. In a cohort of 61,319 Norwegian women interviewed in 1956–1959, the authors analyzed associations between age at menarche and all-cause mortality. A total of 36,114 women died during the 37 years of follow-up. An inverse association was found between age at menarche and the all-cause mortality rate ($p < 0.001$), with an approximately 2.4% (95% confidence interval: 1.6, 3.1) reduced mortality per year increase in age at menarche. The association was stronger in women with an attained age of less than 70 years (3.9% reduction in mortality) than in women aged 80 years and above (1.5%). The inverse association could not be explained by extreme mortality rates in women with very early (10 years) or late (19 years) menarche or by possible confounding variables such as birth cohort, place of residence, occupational category (own or husband's occupation), body mass index, age at first delivery, or parity. Because of lack of data, residual confounding by physical activity or cigarette smoking could not be ruled out. Women with a menarche at age 18 years or later had, however, a slightly higher mortality rate than was predicted by the linear association.

menarche; mortality; prospective studies; puberty

Abbreviation: BMI, body mass index.

The menarche signals the start of the reproductive period of a woman. Still, relatively little is known concerning associations between age at menarche and later morbidity and mortality. Previous studies have shown an inverse association with breast cancer risk (1, 2) and inconsistent associations with the incidence of some other cancers (3–10). Most studies have not found any significant associations between age at menarche and risk of coronary heart disease (11–15), whereas conflicting results have recently been reported for stroke risk (15, 16). Age at menarche may also be associated with other fatal diseases and with conditions such as hip fracture (17).

We are unaware, however, of any study exploring the association between age at menarche and total mortality. The aim of the present study was to describe this association in a 37-year follow-up of more than 60,000 women who were interviewed about age at menarche in the 1950s. More than half of the cohort died during the follow-up.

MATERIALS AND METHODS

During 1956–1959, all women aged 20–69 years by January 1, 1956, in four counties in Norway were invited to a screening program for early diagnosis of breast cancer. Attending women were interviewed according to a standard questionnaire and had a clinical breast examination carried out by a physician. In addition to demographic data, the interview elicited information on different reproductive variables (i.e., age at menarche and menopause, number of full-term pregnancies, age at first and last birth, number of

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abortions, and duration of lactation). Age at menarche was defined as age at first menstruation (e.g., 14 years covers the interval between 14 and 15 years since birth). Furthermore, a history of breast disease or diseases of the genital organs was registered.

Because of low attendance in one county in which the program originally was organized as a pilot project, the current study was confined to women in the three counties Vestfold, Aust-Agder, and Nord-Trøndelag who were 27–69 years of age by January 1, 1956, totaling 92,573 women. The personal registration number was introduced in Norway in 1964, and all residents alive at the census in November 1960 were assigned this unique identification number. Demographic characteristics (obtained from the local population registries) were available for 89,616 women, and the personal registration number was retrieved for 85,063 of these women who were alive at the start of follow-up on January 1, 1961 (i.e., aged 32–74 years). Of these, 63,090 women had attended the screening (74 percent response rate). The response rate was higher in married women, in younger age groups, in rural areas, among people occupied in farming or forestry, and in the county of Nord-Trøndelag where the screening program was offered three times (1, 18). The breast cancer screening program was initiated and organized by the Norwegian Cancer Society. The data about age at menarche and other variables included in our analysis were collected before ethics committees were established. However, the follow-up study was approved by the Norwegian Data Inspectorate, which considered the legal and ethical issues of the study.

A total of 61,361 women stated their age at menarche, but we excluded 42 women whose recorded age at menarche was 20 years or above. Thus, 61,319 women were included in our analysis.

Information on height and weight was available for 48,735 of the 61,319 women, derived from separate measurements made during the period 1963–1975 as part of a compulsory mass examination for tuberculosis. Body mass index was defined as weight (kg)/height (m)^2.

Associations between age at menarche and some reproductive and demographic factors were explored in an analysis of variance with age at menarche as the dependent variable.

The official personal registration number served as a unique identification of each woman, linking our data about age at menarche to information on vital status and cause of death obtained from files kept at Statistics Norway, Oslo. Follow-up started on January 1, 1961, when the personal registration number was introduced. During the complete follow-up through 1997, 36,114 women died.

Associations between age at menarche and the mortality rate were investigated in a Cox proportional hazards regression model by use of attained age (divided into 60-day periods) as the time variable. Women who were alive at the end of follow-up were censored on December 31, 1997. Women who emigrated were censored on the day they left Norway. In all analyses, we adjusted for birth cohort (1886–1889, 1890–1894, 1895–1899, 1900–1904, 1905–1909, 1910–1914, 1915–1928).

Age at menarche was first categorized into eight groups: ages 10 and 11, 12, 13, 14, 15, 16, 17, and 18–19 years. In the main analyses, however, the two lowest and the two highest categories were merged. On the basis of this categorization, we estimated the mean change in mortality associated with a category-higher menarche group.

Body mass index and body height were adjusted for in separate analyses restricted to women with information about height and weight and with follow-up starting January 1, the year after the measurements were made.

We performed the analyses in three predetermined age groups, less than 70 years, 70–79 years, and 80 years or above, and other analyses were carried out within subgroups defined by demographic and reproductive variables.

All tests for specific parameters were two sided. A p value of less than or equal to 0.05 was considered statistically significant. However, the large number of deaths included in our analyses makes very minor differences nominally statistically significant. Furthermore, the large number of stratified analyses conducted increases the likelihood of observing statistically significant differences due to chance alone.

All analyses were performed using SAS software (19).

RESULTS

The mean and median ages at menarche in the women included in our analysis were 14.2 (standard deviation: 1.4) and 14 years, respectively. A total of 1.6 percent of the women experienced menarche when they were 10 or 11 years of age, and 2.0 percent had menarche when they were 18 or 19 years of age. The mean age at the start of follow-up was 49.4 (range: 32–74) years. Approximately 38 percent of the women were aged 44 years or below at the start of follow-up, 29 percent were aged 45–54 years, 22 percent were aged 55–64 years, and 11 percent were aged 65–74 years. The mean follow-up period was 28.4 years (range: 0–37 years).

Table 1 shows associations between the mean age at menarche and birth cohort and occupational group (own or husband's). There was a linear inverse association between the mean age at menarche and the birth cohort ($p < 0.001$). The proportion of women aged 17 years or above at menarche fell from 10.1 percent in women born in 1886–1889 to 3.9 percent in women born in 1920–1928. Differences in the mean age at menarche were observed between women in the separate occupational groups ($p_{homogeneity} < 0.001$), but the maximal difference was only approximately 2.5 months and 2 months when adjusted for birth cohort. Women who had their first child when they were less than 23 years of age reported that they had experienced their menarche approximately 4 months (3 months when adjusted for birth cohort) earlier than women who had their first child when they were above 28 years of age ($p < 0.001$). Women who were obese (body mass index (BMI): ≥ 30 kg/m^2) reported an approximately 7 months earlier menarche than did women with a normal weight (BMI: <25 kg/m^2) ($p < 0.001$) (results not shown in table).

The major causes of death in this cohort were ischemic heart disease, stroke, and cancer (table 2). Violent deaths represented only 3 percent of the deaths.

TABLE 1. Associations between age at menarche and birth cohort and occupational group in a 37-year follow-up of 61,319 Norwegian women, 1961–1997

	No. of women	Mean age (years) at menarche
All women	61,319	14.2 (1.4)*
Birth cohort		
1886–1889	1,672	14.6 (1.5)
1890–1894	4,059	14.6 (1.5)
1895–1899	5,825	14.5 (1.5)
1900–1904	7,093	14.5 (1.5)
1905–1909	8,117	14.3 (1.4)
1910–1914	9,174	14.2 (1.4)
1915–1919	9,430	14.1 (1.4)
1920–1924	9,706	14.0 (1.3)
1925–1928	6,243	13.9 (1.4)
Occupational category		
Professional, private enterprise	9,553	14.2 (1.4)
Clerical work	7,540	14.1 (1.3)
Fishing, ship officers, crew	5,293	14.3 (1.4)
Farm and forestry work	13,175	14.3 (1.4)
Industrial work	7,593	14.3 (1.4)
Domestic and other work	10,770	14.3 (1.4)
Not specified	7,395	14.3 (1.5)

* Numbers in parentheses, standard deviation.

Table 3 describes the association between age at menarche and total mortality adjusted for birth cohort, with age at menarche categorized into eight groups. Although the general association is an inverse relation, there was also an indication of a higher mortality in women with a very late menarche (18 or 19 years of age). The point estimate for women aged 18 and 19 years at menarche showed only marginal statistical difference ($p = 0.05$) from that of women aged 17 years at menarche.

Further adjustments with a more detailed categorization of birth cohort (1886–1889, 1890–1894, 1895–1899, 1900–1904, 1905–1909, 1910–1914, 1915–1919, 1920–1924, 1925–1928) or for the variables ever been married, occupation, county of residence, parity (0, 1, 2, 3, 4, 5, >5 children), or age at first delivery in parous women did not essentially influence the results. An analysis with adjustments for all of these possible confounders performed in concert confirmed that the association was virtually unaffected. If anything, the increased mortality in women with an early menarche was slightly strengthened. Furthermore, adjustment for body mass index (categorized into low weight (BMI: <20 kg/m^2), normal weight (BMI: 20–<25 kg/m^2), overweight (BMI: 25–<30 kg/m^2), and obesity (BMI: ≥30 kg/m^2)) or height (categorized into intervals ≤155 cm, 156–160 cm, 161–165 cm, and ≥166 cm) did only marginally influence the association between age at menarche and total mortality displayed in table 3.

TABLE 2. Main causes of death during a 37-year follow-up of 61,319 Norwegian women, 1961–1997

Cause of death	No. of deaths	% of all deaths
Ischemic heart disease	7,655	21.2
Stroke	6,074	16.8
Total cancer	7,861	21.8
Other diseases	13,092	36.3
Violent deaths	1,214	3.4
Unknown cause	218	0.6
All deaths	36,114	100.0

In a model including both a linear and a second-order term for age at menarche as well as a linear term for birth cohort, the second-order term for age at menarche was statistically highly significant ($p < 0.001$). When stratified by birth cohort (1886–1899, 1900–1914, 1915–1928), the inverse J-shaped association was retained in all three birth cohort groups, although the second-order term was not statistically significant in women born before 1900 and in women born in 1900–1914 ($p = 0.51$ and 0.09, respectively).

In a separate analysis, we excluded women with a very early (aged 10) and late (aged 19 years) menarche (together representing 0.6 percent of the women). The mortality rate ratio among women aged 11 years at menarche was 1.16 (95 percent confidence interval: 1.06, 1.27), and that associated with women aged 18 years at menarche was 0.99 (95 percent confidence interval: 0.92, 1.07) when women aged 14 at menarche represented the referent category. Thus, the linear trend was confirmed and somewhat strengthened.

Table 4 displays the results when the women with very early and late menarche are combined with the women aged 12 and 17 years at menarche, respectively. A second-order term was still significant ($p \leq 0.03$) in analyses for all women, as well as in analyses including women with an attained age of less than 80 years, but inspection of the point estimates in table 4 suggests that it is correct to describe the association as a predominantly linear one. The table also demonstrates that there is a linear interaction ($p = 0.017$) with attained age. In women with an attained age of less than 70 years, a 1-year increase in age at menarche was associated with a nearly 4 percent reduction in total mortality, whereas in women aged 80 years or above, it was associated with a 1.5 percent reduction in mortality.

We also performed a number of stratified analyses within subgroups according to birth cohort, county of residence, occupation, menopausal status, parity, abortions, age at first and last birth, and body mass index. As expected from the stratified analysis by attained age (table 4), the association between age at menarche and total mortality tended to be stronger in women born after 1915 than in women born before 1900. The strength of the association did not, however, differ significantly among the three birth cohort groups 1886–1899, 1900–1914, and 1915–1928 ($p_{linear\ trend} = 0.12$). It is worth noting that a statistically significant linear association ($p = 0.009$) with mortality was even found in women born before 1900.

TABLE 3. Total mortality according to age at menarche in a 37-year follow-up of 61,319 Norwegian women, 1961–1997*

Age (years) at menarche	No. of women	Person-years	No. of deaths	Mortality rate ratio	95% confidence interval
≤11	1,003	29,127	574	1.13	1.04, 1.23
12	5,365	156,527	2,976	1.08	1.04, 1.13
13	11,344	336,531	5,977	1.02	0.99, 1.05
14	19,993	572,852	11,412	1.00	Referent
15	13,667	381,635	8,439	0.97	0.94, 0.99
16	6,241	168,180	4,133	0.96	0.93, 1.00
17	2,471	65,135	1,684	0.94	0.89, 0.99
≥18	1,235	30,944	919	1.02	0.95, 1.09
p value for second-order term					<0.001

* Results are adjusted for attained age and birth cohort.

The inverse association observed in the main analysis was found to be very consistent in the different subgroups. However, as one must expect with a large number of stratified analyses, there were subgroups in which we found no statistically significant association between age at menarche and total mortality. Nulliparous women seemed to have a somewhat lower reduction in mortality with increasing age at menarche than did other women, but no significant difference between the categories defined by parity was found ($p = 0.18$).

DISCUSSION

We have previously described the associations between age at natural menopause and total mortality in the same data set (20). In the present report, we study the impact of the starting point of the reproductive period of the woman rather than the end of it. To our knowledge, this is the first study of the possible associations between this very important developmental milestone in the life of a woman and total mortality.

We found age at menarche to be inversely related to total mortality. The association was very consistent in stratified analyses. Overall, 1-year later menarche was associated with a 2–3 percent reduced total mortality. However, we also found that a model with a second-order term for age at menarche was statistically significant, indicating a U- or inverse J-shaped association between age at menarche and total mortality, particularly in women with an attained age of less than 70 years. Thus, a high age at menarche was also associated with an increased mortality. However, although this finding has biologic interest, it is relevant for very few women, as only 2 percent in our population reported to have had their menarche when they were 18 years or older.

It may seem puzzling that a relatively late menarche (15–16 years) and a late menopause (20) are both related to a low

TABLE 4. Total mortality according to age at menarche and attained age in a 37-year follow-up of 61,319 Norwegian women, 1961–1997*

Age (years) at menarche	All women				Women aged <70 years		Women aged 70–79 years		Women aged ≥80 years	
	No. of women	No. of deaths	Mortality rate ratio	95% confidence interval	No. of deaths	Mortality rate ratio	No. of deaths	Mortality rate ratio	No. of deaths	Mortality rate ratio
<13	6,368	3,550	1.09	1.05, 1.13	886	1.14	1,244	1.12	1,420	1.04
13	11,344	5,977	1.02	0.99, 1.05	1,418	1.01	2,126	1.06	2,433	0.99
14	19,993	11,412	1.00	Referent	2,387	1.00	3,793	1.00	5,232	1.00
15	13,667	8,439	0.97	0.94, 0.99	1,470	0.93	2,780	0.99	4,189	0.96
16	6,241	4,133	0.96	0.93, 1.00	645	0.92	1,314	0.96	2,174	0.97
>16	3,706	2,603	0.97	0.93, 1.01	381	0.96	822	0.99	1,400	0.95
Mean % reduction in mortality†			2.4 (1.6, 3.1)		3.9 (2.2, 5.6)		2.8 (1.4, 4.1)		1.5 (0.4, 2.6)	
$p_{linear\ trend}$			<0.001		<0.001		<0.001		0.01	

* Results are adjusted for attained age and birth cohort.
† The mean percentage of reduction in mortality associated with a category-higher menarche age group (95% confidence interval).

mortality. The finding for menarche is the opposite of what we would expect if cumulative exposure to female sex hormones was associated with a low total mortality. Within another framework, however, our results for age at menarche and natural menopause may be in accordance. They both indicate that women who are biologically younger than their chronologic age would suggest (have a late menarche or a late natural menopause) have a lower mortality than do women with an average age at menarche or menopause. This has previously been suggested for age at natural menopause (21).

The impact of a 1-year change in age at menarche on total mortality (3.9 percent in the analysis including women aged <70 years) is considerably larger than the effect of a similar change in age at menopause (1.2 percent) (20). In order to obtain a better understanding of how age at menarche influences mortality, it is necessary to analyze cause-specific mortality. A 2–3 percent reduction in total mortality associated with a 1-year increase in age at menarche cannot be considered negligible at the population level. For the individual woman, however, the reduction of the absolute mortality rate (5 per 10,000 person-years) may be of marginal importance.

The effect of age at menarche on total mortality is attenuated with increasing age. This may reflect the longer time since the relevant exposure. A more likely explanation is that the relative importance of any particular risk factor is reduced with increasing age-related mortality.

The mean age at menarche among the women included in our study (14.2 years) was rather high compared with what is expected today. In most Western countries, the mean menarcheal age is now between 12.5 and 13 years (22–25). In a European study, the mean age at menarche was found to differ between countries, with the highest mean in the Scandinavian countries Sweden and Denmark and the lowest in Italy: 13.6 years in both Sweden and Denmark and 12.5 years in Italy (22). Norwegian data were unfortunately not included.

The prospective design of our study makes biased reporting of age at menarche unlikely. No study of the validity and reproducibility of the data about age at menarche was conducted within this cohort, but other studies have found that most women are able to recall the age at menarche with relatively high validity (26, 27) and reproducibility (25, 28, 29). However, as the women when interviewed must recall an event (albeit important) that happened many years ago, some random misclassification of age at menarche is inevitable.

Body weight is linked to both age at menarche (30–32) and mortality (33, 34). We have, unfortunately, no data about the body weight of the women during the years before menarche. However, body mass index measured at one point in time is strongly correlated to body mass index measured many years later (35, 36). We have adjusted for body mass index measured incidentally during follow-up. The adjustment did not influence the association, which was confirmed in stratified analyses.

It has previously been found that the age at menarche is directly related to the age at which a woman marries and delivers her first child (37). The latter relation was also found in our population, but our analyses confirmed that age at first delivery was not a confounder.

It is well known that physical activity, especially of some intensity, tends to delay menarche (38–40) and that physical activity reduces mortality. We have no data on such activities, not even in adulthood. In a population-based study in Tromsø, Norway, in 1994–1995, the association between age at menarche and physical activity was examined in more than 1,800 women born in 1928 or before. A weak ($r = 0.04$) positive association was found in these elderly women between age at menarche and frequency of low intensity (not sweating or short of breath) physical activity ($p = 0.03$ after adjustments for age) (unpublished data). Therefore, we cannot totally exclude confounding by physical activity, although the association between age at menarche and physical activity was weak, and some of the confounders that we have adjusted or stratified for (as occupational status and age) can to some extent serve as proxy variables for physical activity.

Information about smoking was not collected when the women were interviewed in the 1950s. On the basis of national data (41), we estimated that approximately 30 percent of Norwegian women with a distribution over birth cohorts as displayed in table 1 have ever smoked. Smoking at the age of 15–19 years was rare, however, approximately 4 percent. The percentage of smokers among the women included in our study, living predominantly in a rural environment, was certainly lower than in more urban parts of the country (42). We are not aware of published Norwegian data concerning possible correlations between smoking and age at menarche in the relevant birth cohorts. Data from the Tromsø Study in northern Norway show no association ($p = 0.9$) between smoking history (current, former, and never smoking) and mean age at menarche in more than 1,800 women born in 1928 or before. There were, however, some indications of a higher prevalence of ever smoking in women with very low or very high age at menarche (unpublished data). The relevance of these findings to the women included in the analysis of the associations between age at menarche and mortality may be questioned, as the Tromsø women had a substantially higher prevalence of ever smoking (46 percent) than estimated from national data (30 percent), and they were on average born 10 years later and lived in another part of Norway. It would, however, be presumptuous to totally exclude smoking as a potential confounder in our analyses.

In a recent study from the United States, women who reported a menarche before the age of 10 years or after the age of 17 years were excluded from the analyses (25). An extreme age at menarche may reflect medical conditions influencing mortality. Nutritional deficiencies associated with chronic illness (e.g., inflammatory bowel disease) and general malnutrition may also delay menarche (24). The latter may be relevant for some of the women in our cohort as they had their menarche when Norway was still a rather poor country. These women, raised in poverty, may have experienced increased mortality in adulthood. It is also known that anorexia nervosa and diabetes both delay menarche (24, 25). Unfortunately, no information about such conditions was available. Thus, chronic diseases may contribute to an explanation of the somewhat higher mortality in the small group of women aged 18 or 19 years at menarche

but not to the main finding of our analyses, the inverse association between age at menarche and all-cause mortality. Exclusion of women with very early (aged 10 years) and late (aged 19 years) menarche did, if anything, strengthen the inverse association between menarcheal age and total mortality. This was even more the case if women aged 18 years at menarche were also excluded. Thus, there is no indication that our main result is due to disease among women with extreme values for age at menarche.

In summary, in this large cohort of Norwegian women followed for 37 years, we found an inverse association between age at menarche and total mortality. Women who experienced menarche when they were 10 or 11 years of age had approximately 10 percent higher mortality in later life than did women with a median value of age at menarche in our study population (14 years).

ACKNOWLEDGMENTS

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