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Prenatal and infant exposures and age at menarche

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Abstract

Background—Early menarche is related to increased risk of breast cancer. The number of established factors that contribute to early menarche is limited. We studied prenatal and infant exposures in relation to age at menarche in a nationwide cohort of women who have a family history of breast cancer.

Methods—The study comprised 33,501 women in the Sister Study who were aged 35–59 years at baseline (2003–2009). We used polytomous logistic regression to estimate separate relative risk ratios (rRRs) and 95% confidence intervals (CIs) for associations of self-reported exposures with menarche at 10, 11, 14, and 15 years relative to menarche at 12–13 years.

Results—Early menarche (10 or 11 years) was associated with having low birth weight, having had a teenage mother, being firstborn, and specific maternal prenatal exposures: smoking, DES (diethylstilbestrol), pre-pregnancy diabetes, and pregnancy-related hypertensive disorder. Prenatal exposures most strongly associated with very early menarche (10 years) were DES (rRR = 1.56 [95% CI = 1.24–1.96]), maternal pre-pregnancy diabetes (2.24 [1.37–3.68]), and pregnancy-related hypertensive disorder (1.45 [1.18–1.79]). Soy formula was associated with both very early menarche (1.21 [0.94–1.54]) and late menarche (14 years: 1.17 [0.98–1.40] or 15 years: 1.28 [1.06–1.56]).

Conclusions—Although menarche is only one marker of pubertal development, it is a commonly used surrogate. The observed associations of prenatal DES and soy formula exposure with age at menarche are consistent with animal data on exogenous estrogens and pubertal timing. Early-life exposures may confound associations between age at menarche and hormonally dependent outcomes in adults.

Age at menarche is a frequently used marker of puberty that has been related to later health. Early menarche (11 years) has been associated with increased risk of breast cancer, adult obesity, type 2 diabetes, metabolic syndrome, and other markers of cardiovascular disease.^{1,2} Mean age at menarche in the United States decreased from the late 1800s to the 1950s, although it is unclear whether a decline has continued since the 1950s.³ A younger mean age at menarche in the United States compared with Japan may partially explain the

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historically higher US breast cancer rates.⁴ In US girls, blacks and Hispanics have been reported to experience earlier menarche than whites.^{5,6}

Maternal age at menarche and childhood adiposity have been consistently associated with age at menarche.^{1,7} Prenatal exposure to maternal smoking⁸⁻¹⁴ and body size at birth, especially birth weight,^{11,12,15-25} have been widely studied in relation to age at menarche, with inconsistent results. Studies in mice suggest that pubertal timing can be affected by exogenous estrogens including diethylstilbestrol (DES) and genistein, one of the key isoflavones in soy formula.²⁶⁻²⁸ Maternal pre-pregnancy or gestational diabetes have been linked with later childhood obesity,²⁹⁻³¹ but no study has examined whether maternal diabetes influences daughter's age at menarche.

We evaluated whether prenatal and other early-life exposures were associated with age at menarche, using a large sample of U.S. and Puerto Rican women.

MATERIALS AND METHODS

Study population

The Sister Study is a prospective cohort study that enrolled 50,884 US and Puerto Rican volunteers from 2003 to 2009, with follow-up for breast cancer and other health conditions. Eligible women were ages 35 to 74, had never been diagnosed with breast cancer, and had a full or half-sister diagnosed with breast cancer. The Sister Study was approved by the Institutional Review Board (IRB) of the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health and the Copernicus Group IRB. Further study details are provided elsewhere.³²

Participants completed computer-assisted telephone interviews on possible risk factors for breast cancer and other conditions. Sister Study investigators were interested in whether early-life exposures affected risk of breast cancer and other health conditions; therefore, the participants also completed a self-administered family history questionnaire including early-life exposures that women could reasonably report retrospectively. A pre-paid phone card was provided to participants to encourage them to contact their mother or other relatives for assistance; however, we do not know whether participants contacted relatives or consulted birth records before completing family history questionnaires.

We analyzed baseline data from the 34,208 women who were aged 35 to 59 years. We excluded women older than 59 years because their mothers were more likely to be deceased or otherwise unable to inform their daughter about early-life events. Our final study sample consisted of 33,501 women, after further excluding 24 with unknown age at menarche, 676 with missing family history questionnaires on early-life events, and 7 with missing race/ethnicity data.

Age at menarche

Women were asked during the telephone interview how old (years and months) they were when they had their first menstrual period. Ages were truncated at years because fewer than 5% of women reported a value for months. For women who did not know their age at menarche, it was estimated from their grade in school at the time of their first menstrual period (n=77) or from reporting whether their first menstrual period occurred before, after, or at the same time as other girls their age (n=63). The latter responses were estimated as 11 years, 14 years, and 12.5 years, respectively.

Exposures and covariates

Early-life exposures were reported on the self-administered family history questionnaire. Participant factors were birth weight (pounds/ounces), gestational age at birth (categorical), single/multiple birth, having ever been breastfed, and having ever consumed soy formula during infancy. Maternal factors were age at the participant's birth and mother's exposures during the index pregnancy (pregnancy with the participant): living or working on a farm, smoking, DES use, diabetes (pre-pregnancy or gestational), and pregnancy-related hypertensive disorder (preeclampsia or gestational hypertension). Response categories (definitely, probably, probably not, and definitely not) allowed for additional uncertainty for infancy feeding and maternal factors, with the exception of mother's age at the participant's birth. We defined mothers as having gestational diabetes if there was reporting of "pregnancy-related diabetes" and no reporting of diabetes before the index pregnancy. We considered mothers as having gestational hypertension if "pregnancy-related high blood pressure" was reported, and preeclampsia was not reported. Data on maternal hypertension before the index pregnancy was not available.

We classified birth order using sibling birth dates reported by the participant in the family history questionnaire (brothers) and the computer-assisted telephone interview (sisters). Participant date of birth, education, and childhood factors (height and weight relative to peers at age 10, plus family income level [poor, low, middle, or well off]) were reported during the telephone interview.

Statistical analyses

We used polytomous logistic regression to estimate relative risk ratios (rRRs) with 95% confidence intervals (CIs)³³ for each early-life exposure in association with very early (10 years), early (11 years), late (14 years), and very late (15 years) menarche relative to typical ages at menarche (12-13 years). We combined women who reported "definitely" and "probably" for prenatal and infancy feeding exposures to estimate their associations with age at menarche compared with women who reported "probably not" or "definitely not". We initially examined age at menarche associations separately across all birth-order groups and 5-year maternal age categories (data not shown) and then combined categories having similar frequency of early and late menarche for reporting associations. Birth weight was categorized in clinically relevant categories: <2,500 g (low), 2,500-3,999 g (reference), and 4,000 g (high). Because there was no difference in age at menarche for high versus reference birth weight (data not shown), we further combined those two categories. All polytomous logistic regression models included race-ethnicity, participant's birth decade, and childhood family income as confounders because they may influence the exposures and age at menarche. Models also included categorical interaction terms for race/ethnicity and birth decade to more fully adjust for confounding by these variables. We did not consider relative height or weight at age 10 as confounders because body size could be on a causal pathway between exposures and age at menarche, and neither factor could be a cause of earlier exposures. We conducted analyses using SAS V9.2 (SAS Institute Inc., Cary, NC).

Because there was a high proportion of missing data for some exposures, we performed secondary analyses in which we repeated the main analyses after multiple imputation of missing data (eTable). We assumed data were missing at random (dependent on values of other nonmissing variables but not on values of missing variables). We did multiple imputation by chained equations (MICE) using IVEWARE V0.1 (University of Michigan, Ann Arbor, MI) within SAS software.^{34,35} We did 10 imputations of missing data, and included all early-life exposures, race/ethnicity, birth decade, race/ethnicity-by-birth-decade interaction terms, childhood family income, participant's education level, maternal death prior to baseline, and age at menarche in the imputation regression models. Even though

mother's vital status and participant's education level were not confounders in our polytomous logistic regression analyses, they were included in the imputation regression models because they influenced whether early-life data were missing. We used PROC MIANALYZE in SAS V9.2 to summarize polytomous logistic regression results across all 10 imputation datasets. In analyses using imputed missing data, we could mutually adjust for related early-life factors to account for the possibility of additional confounding without reducing sample size.

RESULTS

Table 1 shows descriptive characteristics of participants in each menarche category. The frequency of early menarche (< 11 years) was 20% (Table 1), with 7% reporting menarche at 10 years of age or younger. The frequency of late menarche (≥ 14 years) was 24%, with 10% reporting menarche at 15 years of age or older. The trend for the frequency of early menarche across birth decades differed by race/ethnicity (data not shown). Among black and Hispanic women, the percent reporting early menarche increased with birth decade, with more than 35% of women born in 1970-1974 reporting early menarche compared with 27% for those born in 1944-1949. However, we found the opposite pattern for white women or those of other race/ethnicity (Asian or Pacific Islander, Native American, other), with early menarche less common in the most recent birth decade than in earlier decades. Women reporting that their family was poor during childhood had higher frequencies of early menarche than those who reported their family was middle income or well off. As expected from previous literature,¹ women who reported they had been heavier or taller than their peers at 10 years of age had the greatest proportion with early menarche and the lowest proportion with late menarche. These associations for weight and height remained after adjusting for each other and for covariates from the main analyses (e.g., menarche < 10 years: rRR = 2.18 [95% CI = 1.96-2.41] for having been heavier and rRR = 2.05 [1.85-2.27] for having been taller relative to having been similar to peers).

Early-life exposures

Several early-life exposures were associated with greater than 10% relative increases in the occurrence of early or late menarche. Exposures associated with early menarche were having had a teenage mother, being firstborn, having low birth weight, having been born at least one month early, having been fed soy formula, and several maternal factors during the index pregnancy (diabetes, hypertensive disorder, DES use, and smoking) (Table 2). An association was found only with pre-pregnancy diabetes and not with gestational diabetes, whereas associations were similar for the two types of pregnancy-related hypertensive disorders. Associations were generally stronger for very early menarche (< 10 years) than for menarche at 11 years. In particular, associations were found specific to very early menarche for three exposures (DES, rRR = 1.56 [95% CI = 1.24-1.96]; firstborn, 1.18 [1.06-1.32]; and soy formula, 1.21 [0.94-1.54]). Soy formula consumption was also associated with late menarche. Associations with late menarche for having been born at least one month early and multiple birth were specific to very late menarche (≥ 15 years).

Imputation of missing data did not materially change the estimated associations (eTable). Further adjustment for maternal age and firstborn status did not change any of the associations for other early-life exposures, and mutually accounting for both of these exposures in the same model did not affect their associations with age at menarche (data not shown). The association between pregnancy-related hypertensive disorder and early menarche was unchanged by adjustment for multiple birth and maternal diabetes (data not shown). After further adjustment for multiple birth, maternal age, and maternal factors during the index pregnancy (DES, smoking, diabetes, and hypertensive disorder), the association between preterm birth and very early menarche was attenuated (1.10

[0.82-1.47]), although some association with very late menarche remained (1.20 [0.94-1.54]). Adjustment for preterm birth, multiple birth, and maternal factors during the index pregnancy did not affect the association between low birth weight and very early menarche (1.33 [1.08-1.63]). Adjustment for factors indicative of higher-risk pregnancy (multiple birth, maternal diabetes, and maternal hypertensive disorder) did not affect the DES association with very early menarche (1.49 [1.20-1.86]).

Although black and Hispanic women were more likely to report early menarche, their associations between early-life exposures and age at menarche (results not shown) were generally similar to those in the entire cohort. However, analyses for minority subsets were limited by small numbers for rare exposures.

DISCUSSION

Early onset of puberty, which has often been approximated by young age at menarche, can have important implications for conditions diagnosed later in life, such as breast cancer and cardiovascular disease.² Furthermore, animal studies have shown that prenatal and neonatal exposure to exogenous estrogens can alter pubertal timing.²⁶⁻²⁸ We found that several early-life exposures were associated with early menarche: low birth weight, young maternal age at the index birth, firstborn status, soy formula, and maternal exposures during the index pregnancy (pre-pregnancy diabetes, pregnancy-related hypertensive disorder, smoking, and DES use). Associations with low birth weight, pre-pregnancy diabetes, pregnancy-related hypertensive disorder, *in utero* DES, firstborn status, and soy formula were stronger for very early menarche (< 10 years) than for menarche at 11 years. Soy formula, multiple birth, and having been born at least one month early were the only exposures associated with late menarche.

Age at menarche was based exclusively on self-report. Previous reports suggest that there is generally moderate agreement between age at menarche reported in adolescence and later reported by middle-aged women.³⁶⁻³⁸ Classifying women into three categories corresponding to early, typical (12-13 years), and late menarche has been reported to improve validity.³⁷ When our data were categorized in this way, results were largely unchanged (results not shown) except for associations that were specific to very early or very late menarche.

Our large study size allowed examination of associations with several early-life exposures. By using polytomous logistic regression, we could evaluate exposures associated with both early and late menarche. In addition, we could evaluate associations with prenatal exposures that are specific to certain birth cohorts (i.e. DES) or that may have occurred at different rates over time (e.g. smoking). Effects of early-life exposures on age at menarche may be important because early menarche is related to breast cancer and other health conditions in adulthood.² Historical exposures, such as maternal DES use, continue to be relevant for the majority of women at risk for breast cancer today.

By design, the Sister Study enrolled women with a family history of breast cancer in order to enrich the cohort for environmental and genetic risk factors for breast cancer. To the extent that early menarche—a breast cancer risk factor—was more common among our study participants than among women in the general population, the statistical power for estimating associations with early-life exposures would be enhanced.³⁹ In particular, the frequency of early menarche (20%) in our cohort of predominantly white women was lower than in white girls from the Bogalusa Heart Study cohort (30%)⁴⁰ but higher than in white girls from a large clinical study conducted in the 1990s.⁴¹ There is also concern that women with a family history of breast cancer may report age at menarche either more or less

accurately than women without such family history. However, our estimates of mean age at menarche by birth decade for whites (data not shown) were similar to results from the National Health and Nutrition Examination Survey (NHANES).⁴² Furthermore, given that the entire cohort has a family history of breast cancer and all were breast-cancer free when interviewed at baseline, effects on reporting of age at menarche could be expected to be shared across the cohort and unlikely to bias the associations presented.

Misclassification of self-reported exposures is a potential study limitation. We provided phone cards to encourage participants to contact their mothers or other relatives, but we did not ask whether they contacted relatives or consulted records before reporting early-life events. Response categories for some early-life exposures allowed for further uncertainty with reporting. Although not shown, associations with exposures reported as “definite” were generally similar or stronger than those with exposures reported as probable. However, analyses of infancy feeding are limited by the lack of adequate data on duration. For example, the null association with ever having been breastfed may have been influenced by the inclusion of those breastfed for a very short duration.

Because of the large proportion of missing data for some early-life exposures, we repeated our main analyses and considered whether there was additional confounding among early-life exposures after multiple imputation of missing data. Results from these secondary analyses were largely similar to the main analyses and showed little confounding among the early-life exposures. Because maternal vital status at baseline was one of the strongest and most consistent factors that influenced whether data were missing for early-life exposures, we also repeated our main analyses after restricting to the approximately 60% of participants whose mothers were alive at baseline. Results from the restricted subset were less precise, but differences were generally minor except that pre-pregnancy diabetes was no longer associated with very early menarche ($rRR = 1.06$ [95% CI = 0.32-3.56]). However, because having diabetes influences lifespan, our restricted subset had fewer mothers with pre-pregnancy diabetes who were alive at baseline.

Although heavier childhood body weight is a strong predictor of age at menarche,¹ we did not adjust analyses for childhood body weight because it may be on the causal pathway between the exposures and age at menarche. Having been heavier than peers at age 10 was associated with maternal pre-pregnancy diabetes and with prenatal exposure to smoking, while having been lighter than peers at age 10 was associated with having a twin (or triplet) sibling (data not shown), which is consistent with childhood weight being on the causal pathway for age at menarche. However, pregnancy-related hypertensive disorder was weakly associated with both having been lighter and having been heavier than peers at age 10, and low birth weight was strongly associated with having been lighter than peers at age 10.

Although age at menarche does not completely capture pubertal development, our finding that soy formula consumption was associated with both early and late menarche is consistent with animal data suggesting that the dose of genistein influences whether puberty will be advanced or delayed. Mice administered a higher dose of genistein had a delayed vaginal opening (marker of puberty) while mice given a lower dose had an accelerated vaginal opening.²⁶ Neonatal administration of genistein to mice has also produced other alterations in reproductive characteristics, including changes in estrous cycles, early reproductive senescence, and decreased fertility.⁴³ Soy formula delivers a high dose of estrogenic isoflavones to infants per unit body weight⁴⁴; high plasma and urinary concentrations of genistein have been reported in infants fed soy formula.⁴⁴⁻⁴⁶ There are inconsistent results from the two previous epidemiologic studies of soy versus cow milk formula during infancy: one reported no difference in age at menarche,⁴⁷ and the other reported that those given soy

formula early in life (4 months through 6 months of age) had earlier menarche.⁴⁸ Soy formula composition changed in the early 1960s from soy flour to a more highly digestible soy protein isolate,⁴⁹ and so we evaluated whether the association between soy formula and age at menarche differed for women born before and after this time period. The association with late menarche did not change across birth decades, while the association with very early menarche was seen only in those born in 1960 or later (rRR = 1.50 [95% CI = 1.03-2.19]).

In utero DES has been associated with various reproductive abnormalities in women.⁵⁰ In mice, prenatal administration of DES results in an earlier vaginal opening.^{27,28} We found an association of DES with very early menarche (< 10 years of age). Two studies based on documented prenatal DES exposure found no difference in mean age at menarche⁵¹ and no association with early or late age at menarche.⁵² However, these studies did not report on the frequency of very early menarche. Evaluating mean differences in age at menarche may not be sensitive to differences in the frequency of very early menarche because this group typically represents a small proportion of any population (7% in our study sample). Similar to our study findings, Hatch et al.⁵³ reported an association with very early menarche in a cohort study of medically documented *in utero* DES exposure. Information on DES dose and timing during pregnancy was not available in our study.

We found that maternal pre-pregnancy diabetes and pregnancy-related hypertensive disorder were associated with early menarche. Two studies reported no association between prenatal exposure to maternal preeclampsia and age at menarche.^{54,55} However, a large UK cohort study found an earlier mean age at menarche in daughters whose mothers had preeclampsia during their gestation.¹² Prenatal exposure to maternal diabetes has been previously reported to be associated with childhood obesity,²⁹⁻³¹ but we are the first to investigate associations with early menarche in daughters.

Findings from previous studies have been inconsistent for associations with birth order and maternal age at birth.^{10-12,24,56} While the association with firstborn status was specific to very early menarche, we also found an association with early menarche for having had a teenage mother. Even though we adjusted associations for childhood family income, residual confounding may remain because teenage birth is related to poor socioeconomic status. The association with young maternal age at birth may be confounded by the maternal age at menarche because the mother's menarche necessarily preceded her teenage pregnancy with her daughter, and it is known that ages at menarche are correlated for mothers and daughters.⁷ However, we have no data on the age at menarche of the participant's mother. Our finding of an association between having been born from a multiple birth and very late age at menarche is consistent with a large UK cohort study that reported later age at menarche for twins.¹²

Our results are consistent with previous studies that found an association between lower birth weight and early menarche.^{12,15,18,21} However, a few other studies reported associations only with having been small for gestational age^{16,17} or having had lower birth weight and longer birth length.^{19,23} A study of white and Asian girls reported that younger age at menarche was not associated with low birth weight or preterm status, although nonsignificant associations in that direction were present.²⁵ We had a high proportion of women with missing data on gestational age and birth weight. However, after imputation of missing data, adjustment for preterm status did not affect the low birth weight association with early menarche. Associations with low birth weight may be influenced by later growth, but we had only crude data on pre-pubertal growth. In particular, one study reported that the association with birth weight varied by childhood body size.²⁴ Three studies found that subsequent infancy or pre-pubertal growth, but not birth weight, was associated with age at

menarche,^{11,20,22} although two of these studies noted nonsignificant associations between high birth weight and age at menarche after accounting for subsequent growth.^{20,22}

Five previous studies found associations between prenatal exposure to maternal smoking and younger age at menarche,^{8,10-13} with two of these studies reporting associations specifically with smoking in the third trimester¹⁰ and heavy smoking of at least a pack of cigarettes a day.⁸ Two studies in predominantly black or multiethnic cohorts reported an association with later age at menarche and heavy maternal smoking.^{9,14} Although we had no information on smoking frequency or timing during pregnancy, our finding of an association between maternal smoking and early menarche was consistent with other studies in predominantly white cohorts.^{8,10-13} It is also possible that the association with prenatal exposure to smoking may be confounded by maternal age at menarche if mothers with early menarche were more likely to become smokers and have daughters with early menarche. However, associations between prenatal exposure to smoking and early menarche remained in three of the studies after adjustment for maternal age at menarche.^{8,10,11}

Our study adds to prior evidence that early-life exposures influence age at menarche and is the first to report an association with maternal pre-pregnancy diabetes. Besides replication of findings within other study populations, future studies should examine a broader set of pubertal changes beyond age at menarche. Greater understanding of the possible biologic mechanisms that could explain our findings is also an important area for future research. Furthermore, our findings have methodological implications, as early-life factors may confound some of the associations between age at menarche and hormonally-dependent adult outcomes such as breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Adult and Childhood Characteristics by Age at Menarche in Women 35 to 59 Years of Age at Baseline in the Sister Study, 2003–2009 (n = 33,501)^a

Table 1

Characteristic	Age at Menarche (years)					
	10		11		12-13	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Total	2,185 (7)	4,430 (13)	18,950 (57)	4,498 (13)	3,438 (10)	
Race/ethnicity						
Non-Hispanic white	1,579 (6)	3,483 (13)	15,836 (58)	3,841 (14)	2,792 (10)	
Non-Hispanic black	345 (11)	475 (15)	1,724 (53)	331 (10)	383 (12)	
Hispanic	195 (11)	313 (17)	917 (51)	211 (12)	157 (9)	
Other	66 (7)	159 (17)	473 (51)	115 (13)	106 (12)	
Birth year						
1944-1949	408 (7)	831 (14)	3,419 (58)	727 (12)	558 (9)	
1950-1959	1,235 (7)	2,427 (13)	10,555 (57)	2,450 (13)	1,874 (10)	
1960-1969	506 (6)	1,072 (13)	4,632 (55)	1,224 (15)	960 (11)	
1970-1974	36 (6)	100 (16)	344 (55)	97 (16)	46 (7)	
Maternal vital status ^b						
Alive	1,244 (6)	2,604 (13)	11,432 (57)	2,765 (14)	2,148 (11)	
Deceased	934 (7)	1,819 (14)	7,492 (57)	1,721 (13)	1,281 (10)	
Highest level of education ^b						
High school or less	286 (6)	623 (14)	2,520 (56)	597 (13)	488 (11)	
Some college, associate's/ technical degree	811 (7)	1,540 (14)	6,218 (55)	1,528 (13)	1,239 (11)	
Bachelor's	612 (6)	1,216 (13)	5,495 (57)	1,377 (14)	952 (10)	
Graduate	475 (6)	1,051 (13)	4,715 (59)	996 (12)	759 (9)	
Childhood family income ^b						
Poor	208 (9)	325 (14)	1,152 (51)	295 (13)	269 (12)	
Low	573 (7)	1,108 (14)	4,352 (55)	1,047 (13)	826 (10)	
Middle/well off	1,399 (6)	2,990 (13)	13,420 (58)	3,151 (14)	2,332 (10)	
Weight relative to peers at age 10 years ^b						
Heavier	831 (13)	1,257 (19)	3,508 (54)	549 (8)	348 (5)	

Characteristic	Age at Menarche (years)					
	10		11		12-13	
	No.	(%)	No.	(%)	No.	(%)
Same	935	(6)	2,133	(14)	9,144	(60)
Lighter	415	(4)	1,034	(9)	6,260	(54)
Height relative to peers at age 10 years ^b						
Taller	941	(10)	1,533	(16)	5,242	(55)
Same	781	(5)	1,979	(13)	8,988	(59)
Shorter	459	(5)	914	(10)	4,696	(54)

^aExcluded women with missing data for age at menarche (n = 24) or race-ethnicity (n = 7), and those who did not return questionnaires on early-life factors (n = 676).

^bN does not sum to total due to missing data; <1% of data was missing for each of these study characteristics.

Relative Risk Ratios^a for Early and Late Menarche in Association with Early-Life Exposures in Women Aged 35 to 59 years at Baseline in the Sister Study, 2003-2009 (n = 33,501)^b

Table 2

Exposure	No. (%)	10 years	11 years	14 years	15 years
Mother's Pregnancy:					
Diabetes ^{cd}					
Any	343 (1)	1.47 (1.01-2.16)	1.15 (0.84-1.58)	1.09 (0.79-1.51)	1.00 (0.69-1.45)
Pre-pregnancy ^e	154 (<1)	2.24 (1.37-3.68)	1.37 (0.86-2.18)	1.47 (0.92-2.35)	1.04 (0.58-1.85)
Gestational ^e	178 (<1)	0.98 (0.53-1.84)	0.99 (0.63-1.54)	0.77 (0.48-1.25)	0.98 (0.60-1.60)
None ^f	30,169 (99)	1.00	1.00	1.00	1.00
Hypertensive disorder ^{cd}					
Any	1,257 (5)	1.45 (1.18-1.79)	1.21 (1.02-1.43)	0.96 (0.80-1.15)	1.10 (0.91-1.32)
Preeclampsia ^e	643 (2)	1.45 (1.08-1.94)	1.19 (0.94-1.49)	0.98 (0.77-1.25)	1.11 (0.86-1.45)
Gestational hypertension ^e	492 (2)	1.36 (0.98-1.90)	1.28 (0.99-1.66)	0.91 (0.68-1.21)	1.05 (0.78-1.42)
None ^f	25,568 (95)	1.00	1.00	1.00	1.00
DES ^{cd}					
Yes	1,026 (4)	1.56 (1.24-1.96)	0.98 (0.81-1.20)	0.99 (0.82-1.20)	0.94 (0.76-1.18)
No ^f	27,523 (96)	1.00	1.00	1.00	1.00
Smoking ^{cd}					
Yes	11,029 (34)	1.13 (1.03-1.24)	1.13 (1.05-1.21)	1.05 (0.98-1.13)	1.01 (0.93-1.09)
No ^f	21,067 (66)	1.00	1.00	1.00	1.00
Farm ^{cd}					
Work and residence	3,070 (9)	1.08 (0.93-1.26)	1.11 (0.99-1.25)	0.92 (0.82-1.04)	1.02 (0.90-1.17)
Work only	439 (1)	0.81 (0.54-1.22)	0.87 (0.64-1.17)	0.95 (0.70-1.27)	1.22 (0.91-1.63)
Residence only	1,245 (4)	1.00 (0.79-1.26)	0.89 (0.74-1.06)	1.05 (0.89-1.25)	0.98 (0.80-1.19)
None ^f	27,842 (85)	1.00	1.00	1.00	1.00
Age at delivery, years ^c					
<20	1,537 (5)	1.30 (1.08-1.57)	1.20 (1.04-1.40)	0.91 (0.77-1.07)	0.99 (0.83-1.18)

Exposure	No. (%)	10 years rRR (95% CI)	11 years rRR (95% CI)	14 years rRR (95% CI)	15 years rRR (95% CI)
20-34 ^f	25,191 (76)	1.00	1.00	1.00	1.00
35	6,380 (19)	1.00 (0.89-1.12)	1.06 (0.97-1.15)	0.95 (0.87-1.03)	0.84 (0.77-0.93)
Participant:					
Firstborn ^c					
Yes	6,098 (18)	1.18 (1.06-1.32)	1.01 (0.93-1.10)	0.89 (0.81-0.97)	0.94 (0.86-1.04)
No ^f	27,224 (82)	1.00	1.00	1.00	1.00
Low birth weight, <2,500 grams ^c					
Yes	2,466 (10)	1.28 (1.09-1.50)	1.09 (0.96-1.24)	1.02 (0.90-1.16)	1.08 (0.94-1.25)
No ^f	23,427 (90)	1.00	1.00	1.00	1.00
Multiple birth ^c					
Yes	1,141 (3)	1.03 (0.81-1.31)	0.84 (0.70-1.03)	1.03 (0.86-1.23)	1.23 (1.02-1.48)
No ^f	32,285 (97)	1.00	1.00	1.00	1.00
Gestational age at birth ^c					
Born early, 1 months	767 (4)	1.18 (0.89-1.58)	1.08 (0.87-1.35)	1.02 (0.82-1.28)	1.18 (0.93-1.50)
Born early, 2-4 weeks	1,537 (8)	0.95 (0.75-1.19)	0.98 (0.84-1.15)	0.93 (0.79-1.09)	0.77 (0.64-0.94)
Not 2 weeks early ^f	15,828 (87)	1.00	1.00	1.00	1.00
Breastfed ^{cd}					
Ever	12,961 (41)	1.01 (0.92-1.11)	1.00 (0.93-1.08)	1.03 (0.96-1.10)	0.96 (0.89-1.04)
None ^f	18,478 (59)	1.00	1.00	1.00	1.00
Soy formula ^{cd}					
Ever	1,066 (4)	1.21 (0.94-1.54)	0.95 (0.78-1.15)	1.17 (0.98-1.40)	1.28 (1.06-1.56)
None ^f	27,027 (96)	1.00	1.00	1.00	1.00

^aAssociations are relative to menarche at 12-13 years. Each polytomous logistic regression model included: birth decade, race/ethnicity, childhood family income, and categorical interaction terms between birth decade and race/ethnicity. Women with missing data for childhood family income were excluded (n = 54).

^bExcluded women with missing data for age at menarche (n = 24) or race-ethnicity (n = 7), and those who did not return questionnaires on early-life factors (n = 676).

^cNumbers do not sum to total due to missing data.

^d“Definitely” and “probably” were combined as affirmative responses. Negative group represents women reporting “definitely not” or “probably not.”

^cNumbers do not sum to total for diabetes or hypertensive disorders due to missing data.

^fReference category.