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Maternal age at birth and daughters' subsequent childlessness

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STUDY QUESTION: Does maternal age at a daughter's birth predict her subsequent probability of lifelong childlessness?

SUMMARY ANSWER: In this study population, women born to older mothers were more likely to be childless.

WHAT IS KNOWN ALREADY: Although maternal age at childbearing is increasing in many countries, there is limited evidence on whether being born to older parents may influence offspring fertility.

STUDY DESIGN SIZE AND DURATION: This analysis included 43 135 women from the US-based Sister Study, a cohort study of 50 884 sisters of women with breast cancer recruited between 2003 and 2009.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants had no breast cancer at baseline. Women were included in the analytic sample if they were born between 1930 and 1964 and were at least 44 years old at enrolment. Median age when reproductive history was last ascertained was 63.8 years. We estimated relative risks (RR) and 95% CI of lifelong childlessness as a function of maternal age at birth, using multivariable log-binomial models, including total number of siblings, birth order, socioeconomic indicators of the family of origin, race and birth cohort. We examined the association in different subgroups and in a sibling-matched analysis including 802 sister pairs discordant for childlessness.

MAIN RESULTS AND ROLE OF CHANCE: Compared with women born to 20–24-year-old mothers, those born to mothers aged 25–29, 30–34 and ≥35 years were more likely to be childless [RR (95% CI): 1.21 (1.14–1.29), 1.30 (1.22–1.39) and 1.40 (1.31–1.50), respectively]. The association was consistent in strata defined by birth cohort, number of siblings, birth order, and participant's educational level, as well as within sister pairs. Overall, we found weak evidence for an independent contribution of paternal age at birth to the daughter's probability of childlessness.

LIMITATIONS REASONS FOR CAUTION: All participants had at least one sister, and all information was self-reported. We had no knowledge of whether childlessness was intentional and found only a modest association between maternal age at birth and self-reported indicators of infertility. Still, the association with childlessness was highly consistent.

WIDER IMPLICATIONS OF THE FINDING: Given the widespread tendency to delay childbearing, evaluating the influence of maternal age at birth on offspring fertility is a public health priority.

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Key words: maternal age at birth / paternal age at birth / delayed childbirth / childlessness / fertility

Introduction

Since the 1970s, maternal age at first birth has been increasing in many countries, resulting in rising rates of infertility and childlessness (Schmidt *et al.*, 2012; te Velde *et al.*, 2012; Mathews and Hamilton, 2016; OECD, 2016). As more women conceive for the first time when oocyte quality is declining, it is important to ascertain whether being born to an older mother may negatively affect reproductive function. To date, relatively few studies have examined this question, with mixed results. Studies of reconstructed families from Europe have suggested that daughters of older mothers have lower fertility (Gillespie *et al.*, 2013; Smits *et al.*, 2002) and a higher probability of childlessness (Smits *et al.*, 2002). In a study of Canadian women born in 1850–1899, time from marriage to first birth was slightly (though not statistically significantly) longer in daughters of younger and older mothers (Smits *et al.*, 1999); however, time to first birth was not associated with maternal age ≥30 in British men and women born in 1958 (Joffe and Barnes, 2000). In a registry-based Dutch study, individuals whose parents were older when they first had a child were more likely to remain childless (Steenhof and Liefbroer, 2008); however, only older paternal age at birth predicted childlessness in a cohort of men and women from Wisconsin (Fieder and Huber, 2015). Among women attending a fertility clinic, those born to mothers aged ≥39 had a higher risk of menstrual disorders (Smits *et al.*, 1997). In a small study of infertile patients and their fertile siblings, older maternal age predicted infertility only in men (Tarín *et al.*, 2001).

Although the observed intergenerational continuities in fertility behaviour appear to be driven by parental transmission of socioeconomic status, education and values (Kolk, 2014; Liefbroer and Elzinga, 2012), physiologic mechanisms may also play a role. The foetal and early life environment can exert long-lasting effects on reproductive function (Ho *et al.*, 2017; Qian *et al.*, 2015; Sominsky *et al.*, 2015; Zambrano *et al.*, 2014). Global expression profiles in human oocytes vary with age (Steuerwald *et al.*, 2007), and epigenetic alterations in oocytes can persist in the next generation (Ge *et al.*, 2015; Qian *et al.*, 2015). Epigenetic dysregulation may explain the higher risk of neurodevelopmental disorders (Lee and McGrath, 2015; Sandin *et al.*, 2012) and childhood cancers (Johnson *et al.*, 2009; Yip *et al.*, 2006) in children of older parents (Johnson *et al.*, 2009; Perrin *et al.*, 2010). In infants, differential DNA methylation by maternal age has been reported in two studies, although at different loci (Adkins *et al.*, 2011; Markunas *et al.*, 2016).

In this article, we used data from the Sister Study to examine whether daughters of older mothers were more likely to be childless, taking into account several childhood and adult factors known to influence reproductive behaviour.

Materials and Methods

Study population

The Sister Study is a cohort study of 50 884 women from the US and Puerto Rico, enroled between 2003 and 2009. Women were eligible to participate if they were between 35 and 74 years old, had at least one full or half-sister who had had breast cancer, and had not been diagnosed with breast cancer. Participants answered an extensive set of questions through computer-assisted interviews and self-administered questionnaires, including modules about their family of origin, selected childhood exposures, reproductive history, and past and current health conditions. Sister study participants are followed at (approximately) regular intervals, whereupon information on reproductive history, menopause and health status is updated. By design, all participants in the study have at least one sister. More details on the study are provided elsewhere (Sandler *et al.*, in press). Women were eligible for this analysis if they were at least 44 years old at enrolment (so that virtually all would have complete reproductive histories), had been born between 1930 and 1964, and had not been adopted (to increase the likelihood that they could report on their biological mother) (n = 44 792). We additionally excluded 657 women who had not completed the questionnaire that captured family information, and 1000 because of missing data on other key variables (Supplementary Fig. S1). The analytic sample consisted of 43 135 women (96.3% of eligible), including 3389 with at least one other sister in the dataset. Sisters were matched based on full name and date of birth, per the information provided by each participant. In some cases, women who were not sisters may have been matched due to having a common name or because of the extended algorithms allowing for minor discrepancies in spelling or dates.

Childlessness was defined as not having had a live birth. Maternal age at the participant's birth (from now on referred to as maternal age at birth) was reported in years by 92.4% of women and in 5-year categories by 4.1% (imputed as the mid-point of the category (n = 1748)). For the remaining 3.5%, maternal age at birth was based on the mother's year of birth, estimated from her age at the time of the daughter's interview (n = 476), or if she had died, from year of death and age at death, as reported by the daughter (n = 1053).

The Sister Study was approved by the Institutional Review Boards (IRB) of the National Institute of Environmental Health Sciences, National Institutes of Health, and the Copernicus Group; this analysis was approved by the IRB of McGill University Health Centre.

Statistical analysis

All analyses were carried out with Stata 14.2 (College Station, TX, USA). We estimated relative risks (RR) and 95% CI using multivariable log-binomial regression, with a robust variance estimator to account for the correlation among sisters. We examined maternal age at birth as a categorical variable (<20, 20–24, 25–29, 30–34 and 35+ years) and considered the following childhood predictors as covariates: total number of siblings (both full and half siblings, born either before or after the participant), birth order (first, second or higher), indicators of socioeconomic status during childhood (highest household education when the participant was 13 and income level growing up, in categories), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic and other), and 5-year birth cohort. In one model, we included continuous paternal and maternal age at birth; however, given the results and, especially, the high correlation between maternal and paternal age (r = 0.79), we further considered paternal age at birth only in a subanalysis (described in a later section).

After examining maternal age in a model including all women and all covariates, we carried out several subgroup analyses: by birth cohort (1930–1944, 1945–1954 and 1955–1964), number of siblings (1, 2–3 and 4+), and birth order (1, ≥2) (the latter two restricted to women from full-sibling families). To evaluate whether our findings may have been confounded by parental infertility, we performed a subanalysis among third- or later-born daughters of mothers who had had their first child before age 24 (23 was the median age at first birth among the participants' mothers). We then examined the association in strata defined by highest household education when the participant was 13.

After identifying characteristics that differed between women with and without children, we evaluated whether maternal age at birth was associated with never having legally married (this group does not include women who reported that they were living as married), having obtained a postgraduate degree, having unsuccessfully tried to conceive for longer

than 1 year, and having ever taken fertility medications. Based on these results, we carried out sensitivity analyses to assess whether the association between maternal age at birth and childlessness persisted when excluding women who had never married and when stratifying by the participant's education. We further evaluated whether having an older father, relative to the mother, independently contributed to the probability of childlessness (excluding those who had never married). Within each category of maternal age, we divided father's age into two groups, one including the lowest 75% and the other including the highest 25%, thereby generating a 10-level factor variable.

We checked our findings stratifying by daughters' birth order (i.e. ignoring brothers) and in two additional subgroups: (i) women who were at least 56 when reproductive history was last updated and had not received a diagnosis of breast cancer through age 55 and (ii) women who had never married. In two other models, we adjusted for factors that may have affected reproductive development: (i) prenatal exposure to diethylstilbestrol (DES) and maternal smoking during pregnancy (Palmer *et al.*, 2001; Ye *et al.*, 2010), and (ii) feeding as an infant (breastfed or not and soy formula or not, with non-mutually exclusive categories; Jefferson *et al.*, 2012).

For all stratified analyses, which include different sets of covariates, we show estimates (RR and 95% CI) and predictive marginal probabilities of childlessness (in %, obtained with the *margins* command in Stata) only for maternal age at birth.

Finally, to better account for family factors shared among sisters, we used conditional logistic regression to estimate the association between mother's age at birth and childless in 802 pairs of sisters from full sibling families, after excluding 24 pairs because of inconsistencies in number of siblings or mother's age within pairs.

Table I Characteristics of participants, by maternal age at birth. Data are *n* (%).

Characteristic	Mother's age at participant's birth, years				
	<20 *n* = 2014	20–24 *n* = 10 347	25–29 *n* = 13 452	30–34 *n* = 9952	35+ *n* = 7370
Father's age					
≤31	1919 (95.2)	9369 (90.6)	9301 (69.1)	2099 (21.1)	164 (2.2)
32+	61 (3.0)	910 (8.8)	4078 (30.3)	7796 (78.3)	7166 (97.2)
Missing	34 (1.7)	5 (0.6)	73 (0.5)	57 (0.6)	40 (0.5)
Total no. of siblings[a]					
1–2	585 (29.1)	3531 (34.1)	4868 (36.2)	3402 (34.2)	1881 (25.5)
3–4	758 (37.6)	3977 (38.4)	4845 (36.0)	3464 (34.8)	2370 (32.2)
5–6	406 (20.2)	1703 (16.5)	2131 (15.8)	1630 (16.4)	1446 (19.6)
7+	265 (13.2)	1136 (11.0)	1608 (12.0)	1456 (14.6)	1673 (22.7)
Firstborn	1482 (73.6)	4821 (46.6)	3019 (22.4)	887 (8.9)	157 (2.1)
Race/ethnicity					
Non-Hispanic White	1455 (72.2)	8750 (84.6)	11 788 (87.6)	8670 (87.1)	6272 (85.1)
Non-Hispanic Black	345 (17.1)	854 (8.3)	836 (6.2)	681 (6.8)	595 (8.1)
Hispanic	126 (6.3)	449 (4.3)	502 (3.7)	385 (3.9)	339 (4.6)
Other	88 (4.4)	294 (2.8)	326 (2.4)	216 (2.2)	164 (2.2)
Max household education[b]					
<High school	589 (29.3)	1675 (16.2)	2037 (15.1)	1861 (18.7)	2043 (27.7)
High school/GED	975 (48.4)	4377 (42.3)	4719 (35.1)	3263 (32.8)	2264 (30.7)
Some college[c]	293 (14.6)	2080 (20.1)	2640 (19.6)	1876 (18.9)	1288 (17.5)
BA or higher	157 (7.8)	2215 (21.4)	4056 (30.2)	2952 (29.7)	1775 (24.1)
Income growing up[d]					
Well-off	40 (2.0)	504 (4.9)	953 (7.1)	699 (7.0)	498 (6.8)
Middle income	998 (49.6)	6226 (60.2)	8295 (61.7)	6041 (60.7)	4053 (55.0)
Low income	715 (35.5)	2836 (27.4)	3282 (24.4)	2466 (24.8)	2070 (28.1)
Poor	261 (13.0)	781 (7.6)	922 (6.9)	746 (7.5)	749 (10.2)
Birth cohort					
1930–1944	614 (30.5)	3237 (31.3)	4071 (30.3)	2788 (28.0)	1917 (26.0)
1945–1954	860 (42.7)	4513 (43.6)	5989 (44.5)	4319 (43.4)	3026 (41.1)
1955–1964	540 (26.8)	2597 (25.1)	3392 (25.2)	2845 (28.6)	2427 (32.9)
Had no children	256 (12.7)	1576 (15.2)	2444 (18.2)	1918 (19.3)	1462 (19.8)

[a]Includes full and half siblings born before and after the participant.
[b]Highest level of education in the household when participant was 13 years old.
[c]Includes associate degree.
[d]Based on participant's subjective report.

Results

Median age at recruitment in the analysis sample was 56.9 years. Reproductive history was updated in at least one follow-up interview for 99.5% of the women; median age at the latest update was 63.8 (interquartile range: 58.2–70.0; 98% were 50 or older). In total, 7656 women (17.8%) had not had a live birth. Table I shows the characteristics of participants by maternal age at birth. Women born to the youngest mothers were more frequently the firstborn, less frequently non-Hispanic White, and more likely to be from less educated and poorer families. Women born to the oldest mothers were rarely the firstborn, had more siblings, and came from families from both the lowest and highest educational and income levels.

Table II shows the results of the multivariable model including all women in the analytic sample. Maternal age at birth was positively associated with subsequent daughter's childlessness. Firstborn daughters and those born in families with higher parental education were also more likely to not have children, while having more siblings was associated with a lower likelihood of being childless. There was a strong birth cohort effect, with the probability of childlessness increasing rapidly across birth years beginning in the 1940s. When maternal and paternal age at the daughter's birth were included as linear terms in a model including the same predictors shown in Table II, the RR for a 1-year increase was 1.016 (95% CI: 1.010–1.021) for mother's age and 1.006 (95% CI: 1.001, 1.010) for father's age. (Paternal age was further considered only in a subanalysis.)

Figure 1 shows that the association between maternal age and childlessness was consistent across birth cohorts, and in strata based on number of siblings and birth order. The association persisted after restricting the analysis to third or higher order daughters born to mothers who had had their first child before age 24, i.e. in women whose parents likely had no fertility problems (right panel, last model). Stratifying by highest household education when the participant was 13 yielded similar findings (Supplementary Fig. S2).

Compared with women who had had at least one child, those who had none were substantially more likely to have obtained a postgraduate degree (36.8 versus 21.7%), to never have married (22.4 versus 1%), and to self-report as homosexual (5.3 versus 0.3%). They were also more likely to report having taken fertility medications (9.7 versus 6.4%) and having attempted to conceive for >1 year without success (17.3 versus 10.4%; however, 8% of women did not take part in the follow-up interview in which this question was asked, and 5% of those who participated did not answer the question). More childless women reported having been (definitely or probably) prenatally exposed to diethylstilsbestrol (DES) (3.8 versus 2.1%; this information was missing for 15%). There were no differences in household income in the year prior to enrolment (Supplementary Table SI).

Having been born to a mother ≥25 years was associated with a higher probability of never having married (although the absolute risk was low) and of having obtained a postgraduate degree (Supplementary Fig. S3, left). However, older maternal age at the daughter's birth was not associated with having unsuccessfully tried to conceive for longer than 1 year and only weakly with having taken fertility drugs (Supplementary Fig. S3, right; the latter analysis was restricted to women born after 1944).

Although being born to an older mother predicted both never having married and having achieved a higher education, these factors did not explain the association between maternal age at birth and daughter's childlessness (Fig. 2). Given maternal age, the evidence for an additional effect of paternal age at birth was weak.

We checked whether the daughter's birth order (i.e. ignoring brothers) may have affected her reproductive behaviour (as, for example, youngest daughters may have been more likely to be the ones taking care of older parents and consequently delay starting a family). The

Table II Relative risk (RR) and 95% CI of childlessness, all women. Multivariable log-binomial regression.

	% Childless	N	RR	(95% CI)
Mother's age				
<20	12.7	2014	0.84	(0.74–0.95)
20–24	15.2	10 347	(ref)	
25–29	18.2	13 452	1.21	(1.14–1.29)
30–34	19.3	9952	1.30	(1.22–1.39)
35+	19.8	7370	1.40	(1.31–1.50)
Total no. of siblings				
1–2	19.7	14 267	(ref)	
3–4	18.0	15 414	0.88	(0.84–0.93)
5–6	16.1	7316	0.79	(0.74–0.85)
7+	14.6	6138	0.72	(0.67–0.78)
Birth order				
1	17.5	10 366	1.15	(1.08–1.21)
2+	17.8	32 769	(ref)	
Race/ethnicity				
Non-Hispanic White	17.9	36 935	(ref)	
Non-Hispanic Black	17.7	3311	1.08	(0.99–1.17)
Hispanic	15.0	1801	0.93	(0.82–1.04)
Other	15.9	1088	0.93	(0.81–1.07)
Family income level				
Well-off	18.6	2694	0.94	(0.86–1.02)
Middle income	18.6	25 613	(ref)	
Low income	16.7	11 369	1.07	(1.02–1.13)
Poor	14.5	3459	1.05	(0.96–1.15)
Max household education				
<High school	13.5	8205	0.88	(0.82–0.95)
High school/GED	17.0	15 598	(ref)	
Some college	18.2	8177	1.06	(1.00–1.12)
BA or higher	21.6	11 155	1.21	(1.15–1.28)
Birth cohort				
1930–1934	9.5	1526	(ref)	
1935–1939	10.1	4186	1.05	(0.88–1.26)
1940–1944	13.6	6915	1.41	(1.19–1.66)
1945–1949	18.3	8928	1.91	(1.62–2.24)
1950–1954	20.4	9779	2.14	(1.83–2.52)
1955–1959	21.4	8214	2.27	(1.93–2.67)
1960–1964	21.4	3587	2.27	(1.91–2.68)
Observations: 43 135				

(ref) indicates the reference category.

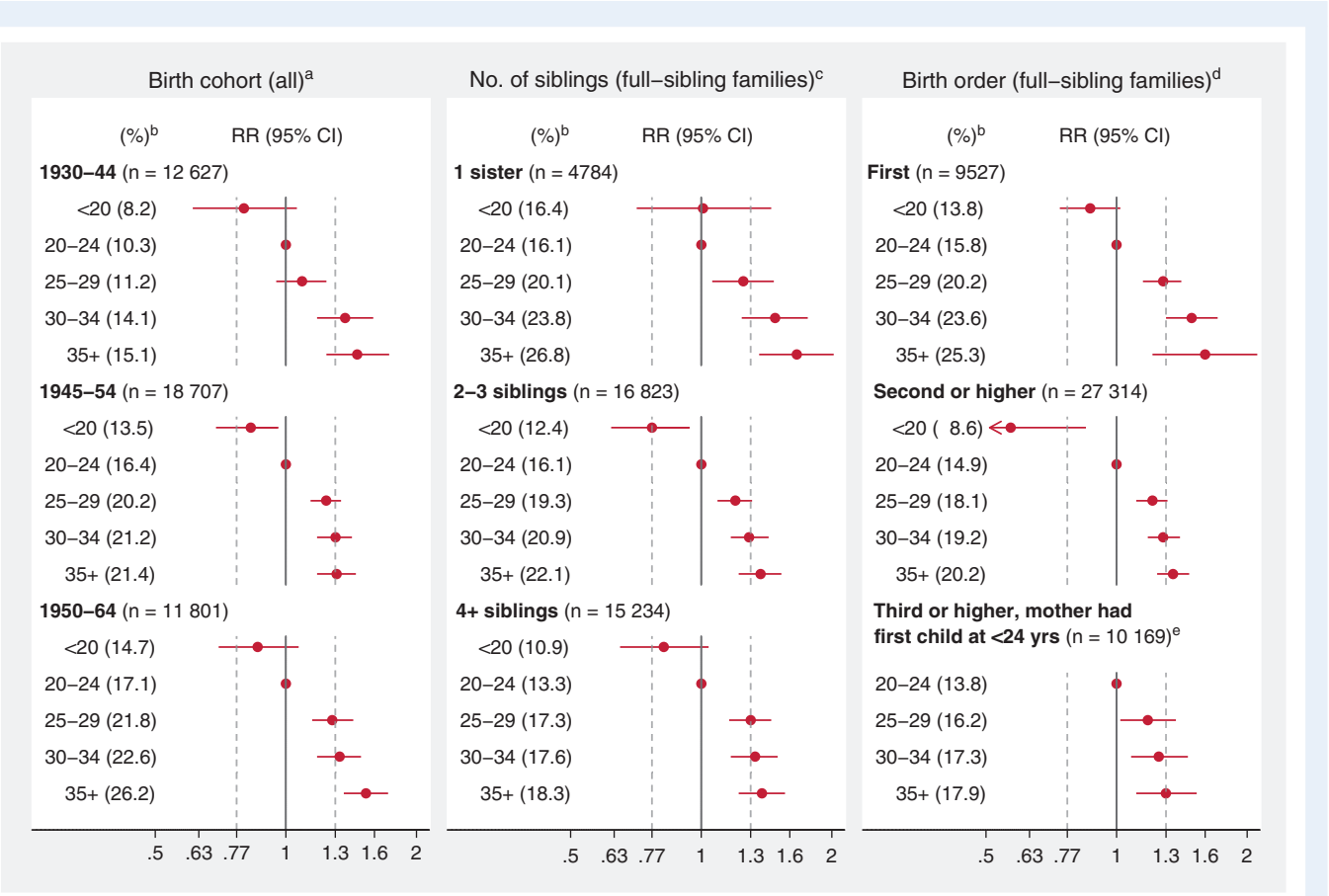

Figure 1 Association between maternal age at birth and childlessness (RR, 95% CI), stratified by birth cohort (left), number of siblings (centre) and birth order (right). Vertical dashed lines at 0.77 and 1.30 are included to facilitate comparisons. [a]Models include: total number of siblings, birth order, race/ethnicity, income level growing up, highest household education when participant was 13, and 5-year birth cohort (see Table II for categories). [b]Adjusted predictive marginal probabilities of childlessness (in %). [c]Analyses restricted to families including only full siblings (defined as those who reported the same number of full and maternal siblings). No. of siblings refers to those born both before and after the participant. Models include the same predictors as in 'a', except for number of siblings. [d]Analyses restricted to families including only full siblings. Models include race/ethnicity, income level growing up, highest household education when participant was 13, and 5-year birth cohort. [e]Analysis restricted to third and higher order daughters born to mothers who had had their first child before age 24. The category of maternal age <20 years was omitted.

association between maternal age at birth ≥35 and childlessness was attenuated in middle daughters (Fig. 3), who, in general, were less likely to be childless. Unsurprisingly, middle daughters had overall more siblings (median: 4, 25th and 75th percentiles: 3 and 6) than oldest and youngest ones (median: 3, 25th and 75th percentiles: 2 and 4 in both groups). The proportion of women ≥35 who went on to have two or more children after the participant's birth was 18.2% among mothers of middle daughters, versus 13.1 and 2.7% among mothers of oldest and youngest daughters, respectively.

The final sensitivity analyses are shown in Supplementary Fig. S4. Results were virtually unchanged when we restricted the analysis to women whose reproductive history was updated at age 56 or later and had no breast cancer diagnosis through age 55. Maternal age at birth was associated with childlessness even in women who had never married, despite the fact that, in this group, 82.3% had no children. Adjusting for prenatal exposure to DES and maternal smoking, or for having been breastfed or given soy formula as an infant did not affect the estimates. Prenatal exposure to DES was associated with a higher probability of childlessness (RR: 1.35, 95% CI: 1.22, 1.49); women who had been breastfed were slightly more likely to be childless (RR: 1.05, 95: CI: 1.00–1.10). Maternal smoking during pregnancy and having been fed soy formula were not associated with childlessness (but only 2.6% of women with non-missing information reported exposure to the latter).

The sibling analysis, based on 802 sister pairs discordant for childlessness, suggested that the odds of childlessness increased with increasing maternal age at birth (P = 0.0013) (Supplementary Table SII). To check whether this association was driven by siblings born several years apart (i.e. potentially confounded by birth cohort effects), we restricted the analysis to pairs born within 5 years of each other. Although the precision of the estimates diminished considerably, the trend remained (Supplementary Table SIII).

Discussion

In this study, women born to older mothers were substantially more likely to be childless. The estimated associations were consistent, on

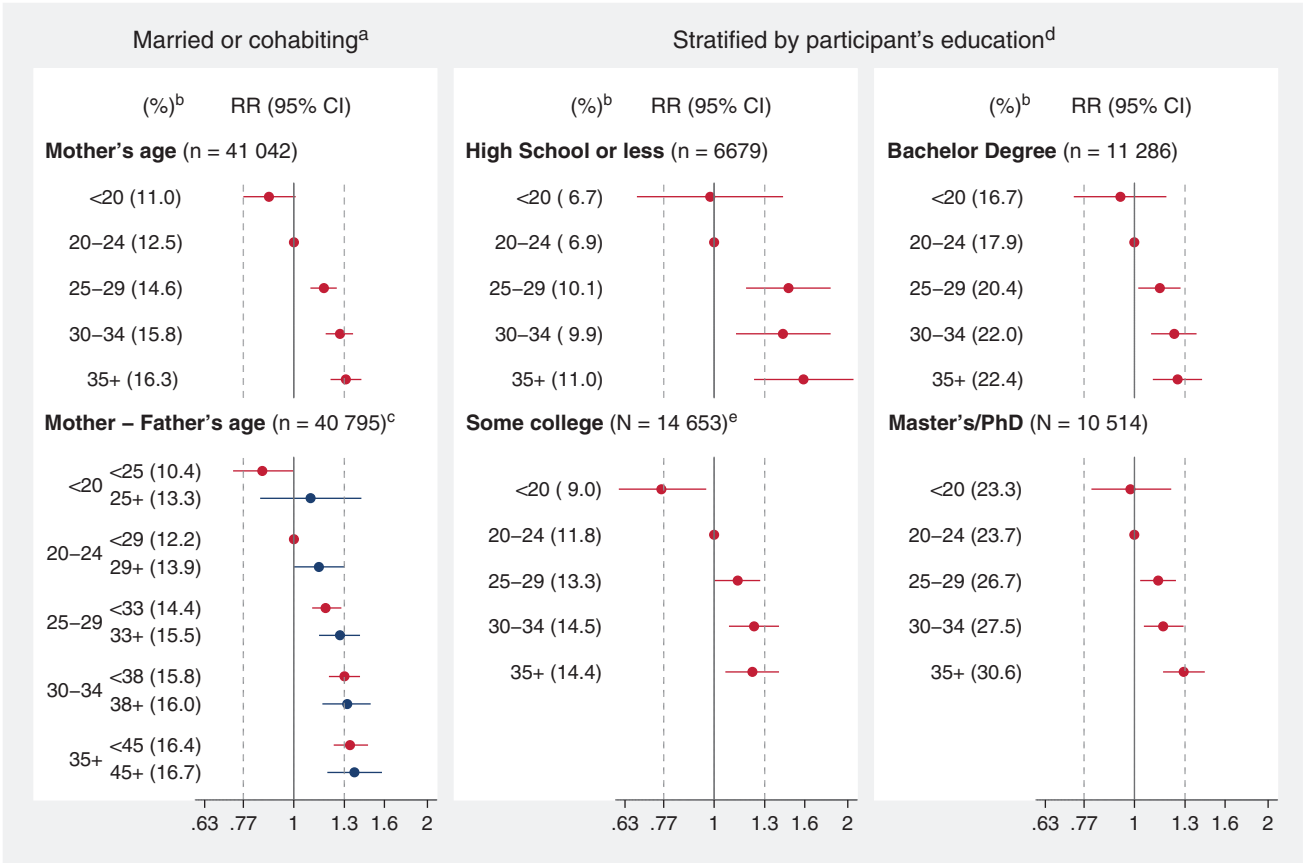

Figure 2 Association between maternal age at birth and childlessness (RR, 95% CI), in analyses restricted to ever married/cohabiting women (left: mother's and combined mother's and father's age) and stratified by participant's education (centre and right). Vertical dashed lines at 0.77 and 1.30 are included to facilitate comparisons. [a]Models include: total number of siblings, birth order (1, ≥2), race/ethnicity, income level growing up, highest household education when participant was 13, and 5-year birth cohort. [b]Adjusted predictive marginal probabilities of childlessness (in %). [c]Mother/father age at birth is modelled as a 10-level factor variable. Older fathers (blue bars) are defined as those in the top quartile of paternal age for each category of maternal age at birth. Paternal age was missing for 247. [d]Models include: total number of siblings, birth order (1, ≥2), race/ethnicity, income level growing up, 5-year birth cohort. [e]Includes associate degree.

the relative scale, across birth cohorts and in strata defined by number of siblings and birth order, despite differences in the absolute probability of childlessness. The association persisted after accounting for not having married and for education, known predictors of childlessness (Hayford, 2013), and after controlling for shared family factors.

In mice, older maternal age has been associated with placental morphological abnormalities and delayed offspring development (Lopes *et al.*, 2009). Pups conceived by older dams and transferred into younger ones at the blastocyst stage had altered growth and impaired cardiometabolic health in the postnatal period (Velazquez *et al.*, 2016). Among mice nurtured by 3-month old foster mothers, hippocampal gene expression and behaviour differed in those born to 18-month old mothers, compared with same-age mice born to 3-month old mothers (Sampino *et al.*, 2017).

Evidence of reduced lifetime reproductive success in offspring of older mothers has been observed in two species of birds (Bouwhuis *et al.*, 2015; Schroeder *et al.*, 2015). In humans, daughters of older mothers have been found to have fewer children or a higher probability of remaining childless in some (Gillespie *et al.*, 2013; Smits *et al.*, 2002; Steenhof and Liefbroer, 2008) but not all (Fieder and Huber, 2015), studies.

The mechanisms by which mother's age at conception and during pregnancy may physiologically influence the daughter's reproductive function are unknown; however, older age is associated with differential gene expression in oocytes (Steuerwald *et al.*, 2007) and may affect the offspring epigenome (Adkins *et al.*, 2011; Markunas *et al.*, 2016). The loci reported as having differential methylation patterns in the first of these studies (Adkins *et al.*, 2011) have not been further corroborated, but the negative correlation between maternal age at daughter's birth and methylation at four CPG sites of KLHL35 found in the later study was replicated in two independent populations (including a subsample of women from the Sister Study) (Markunas *et al.*, 2016).

As we found no association between older maternal age at birth and daughters' reports of trying to conceive for longer than one year, and only a weak association with use of fertility drugs, our data provide limited support for a mechanism acting directly on fecundity. Reproduction is influenced by social, cultural and biological factors. DNA methylation can influence behaviour and is reportedly sensitive to early-life

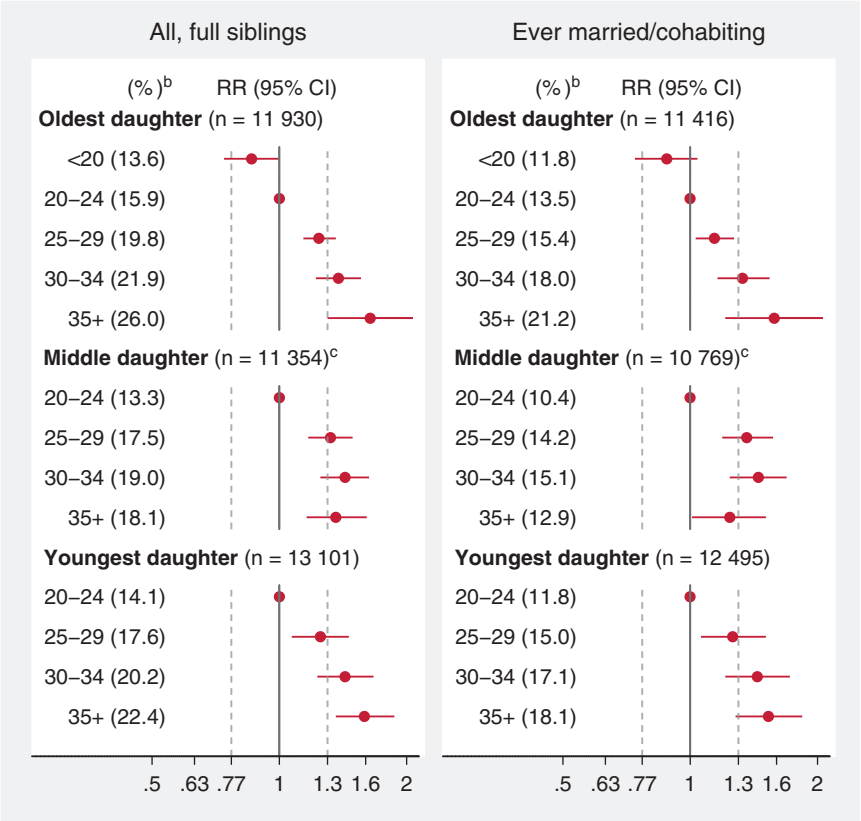

Figure 3 Association between maternal age at birth and childlessness (RR, 95% CI), stratified by daughter's birth order. All women (left) and restricted to ever married/cohabiting women (right). Vertical dashed lines at 0.77 and 1.30 are included to facilitate comparisons. [a]Oldest daughters may be preceded by male children; analogously, youngest daughters may be followed by male children. Models include: no. of older or same-age siblings, (including brothers: 0, 1, 2+ for oldest daughters, and 1, 2, 3+ for middle and youngest daughters), race/ethnicity, highest household education at age 13, income level growing up, and 5-year birth cohort. In total, 215 women were excluded due to missing information on number and birth order of brothers and sisters. [b]Adjusted predictive marginal probabilities of childlessness (in %). [c]Women with a twin sister are included in this category, regardless of birth order.

environmental inputs (Roth, 2013); it is possible that such inputs differ systematically in daughters of older mothers. The available evidence suggests a genetic influence on fecundity, duration of reproductive life and behaviours associated with fertility (Bentzen *et al.*, 2013; Hartge, 2009; Kohler *et al.*, 1999; McCoy *et al.*, 2015). Although higher underlying fecundity may explain the lower probability of childlessness among middle daughters born to older mothers, taken together, our results raise doubts that genetic and socioeconomic factors can entirely explain the observed association.

The main strengths of this study are the large sample size and the wealth of information on childhood and adult characteristics of participants, which enabled us to examine different subgroups with adequate power. In addition, ~98% of the women in the analytic sample were 50 years or older (and all were at least 44) at the latest follow-up, allowing us to capture completed reproductive histories. Several limitations should also be noted. We had no information on whether childlessness was voluntary, and our indicators of clinical infertility were limited. Participants were mostly White and highly educated; consequently, the associations may be different in other populations. All information was self-reported and thus subject to error, particularly for information from the participants' childhood, and possibly for maternal age at birth. Still, differential errors by childlessness seem unlikely. A proportion of women linked as being sisters in the data may not have been related, potentially resulting in artificially wider confidence intervals, as we accounted for clustering in the analysis. Inclusion of unrelated women in the sibling analysis would also result in loss of power. However, we included only pairs with consistent reports of maternal age and number of siblings within pairs, factors that had not been considered in the algorithms used to match putative sisters. By design, this study excluded women who had no siblings and those who had only brothers; furthermore, the fact that all study participants had at least one sister (or half-sister) resulted in the sex ratio of siblings being skewed towards females (1.45:1). Although it has been suggested that having older siblings of the same sex may be associated with lower reproductive fitness (Gillespie *et al.*, 2013; Nitsch *et al.*, 2013), we saw no evidence of such a phenomenon in this population (Supplementary Fig. S5).

In sum, we observed a strong positive correlation between maternal age at birth and daughter's childlessness, remarkably consistent across various subgroups and within sisters. Whether our results are due to

biology, behaviour, or socioeconomic factors -or a combination of these, the possible influence of maternal age on offspring fertility deserves further study, particularly in light of the widespread tendency to delay childbearing. If these findings are replicated in other populations, identifying the underlying mechanism is a public health priority.

Supplementary data

Supplementary data are available at *Human Reproduction* Online.

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Conflict of interest

The authors report no conflict of interest.

Authors' Contributions

O.B. had the idea for this analysis; she carried out the literature search, designed the study, analysed the data, interpreted the results, and wrote the first draft of the article. C.W. is the Sister Study co-principal investigator (PI); she contributed to data acquisition, study design, data analysis and interpretation, and critically revised the article. A.D.'A. is a data analyst of the Sister Study; she contributed to data acquisition and quality control, interpretation of the data, and critically revised the article. D.S. is the Sister Study PI; she contributed to data acquisition, study design, interpretation of the data, and critically revised the article.

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