Annals of Epidemiology 31 (2019) 32–37

Contents lists available at ScienceDirect

Annals of Epidemiology

Original article

Parental age and stillbirth: a population-based cohort of nearly 10 million California deliveries from 1991 to 2011

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ARTICLE INFO

Article history:
Received 4 September 2018
Accepted 1 December 2018
Available online 21 December 2018

Keywords:
Parental age
Advanced maternal age
Advanced paternal age
Stillbirth
Population-based cohort
Perinatal epidemiology

ABSTRACT

Purpose: Parental age at delivery in the United States has been rising. Advanced maternal and paternal ages have been associated with adverse pregnancy outcomes including stillbirth. However, these relationships come from studies that often do not present results for both mother and father concurrently. The purpose of this study was to estimate the risk of stillbirth for maternal and paternal age in the same cohort of deliveries.
Methods: This is a population-based cohort study of all live birth and stillbirth deliveries in California from 1991 to 2011. The individual associations between maternal and paternal ages and stillbirth were estimated with hazard ratios from Cox proportional hazard models. Age was modeled continuously with restricted cubic splines to account for nonlinear relationships. Mean parental age was used as the referent group.
Results: J-shaped associations between maternal and paternal ages were observed in crude models where older mothers and fathers had the highest hazard ratios for stillbirth. In maternal models, after adjusting for maternal and paternal covariates, young maternal age no longer showed increased hazard ratio for stillbirth, whereas the association with older mothers remained. In adjusted paternal models, the relationship between young paternal age and stillbirth was unchanged while the hazard ratio for older fathers was slightly smaller.
Conclusions: After adjusting for both parents' age, education, race/ethnicity, along with parity, older mothers and fathers were independently associated with elevated hazard ratios for stillbirth.

Introduction

Average parental ages at delivery in the United States have been rising. From 1970 to 2016, mean maternal age increased from 24.6 to 28.7 years [1,2]. Mean age at delivery for fathers has also increased from 27.4 to 30.9 years over the last four decades [3]. Both maternal and paternal ages have been associated with adverse pregnancy outcomes [4,5]. Advanced maternal age, usually defined as 35 years and older, has been associated with preterm birth (PTB), stillbirth, preeclampsia, and selected birth defects, including chromosomal anomalies [6–10]. Advanced paternal age, although less studied, has shown some association with stillbirth, low birth weight, PTB, and certain birth defects [9,11–16]. Advanced paternal age has received recent attention owing to its role in the increased occurrence of fetal *de novo* mutations and their potential contribution to disease risk, including PTB [17,18].

Two recent population-based cohort studies observed J-shaped associations between age and stillbirth, with one study investigating maternal age and the other paternal age [10,13]. Each study modeled age as a continuous variable and allowed for nonlinearities in the relationship with stillbirth by use of restricted cubic splines. Such analytic approaches allow the relation between outcome and exposure to possess a flexible curve [19] and remove the reliance on categorizing age into groups, for example, 5-year increments. The two studies, however, involve differing populations, British Columbia and

The authors have no potential conflicts of interest to declare.
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https://doi.org/10.1016/j.annepidem.2018.12.001
1047-2797/

Denmark, and neither simultaneously presented age-related risks for both mothers and fathers.

To extend the limited data in this area of potential reproductive effects of advanced age, our objective of the present study was to estimate the risk of stillbirth for maternal and paternal age, simultaneously, in a population-based cohort of approximately 10 million California births from 1991 to 2011.

Methods

Data

Data for this study come from the 1991–2011 California linked Birth Cohort Files. These files contain merged birth, fetal death, and infant death certificates for all vital records in California with Office of Statewide Health Planning and Development (OSHPD) maternal and infant hospital discharge data 9 months before delivery, at delivery, and up to 1 year after delivery. The linkage used to assemble the birth cohort is accurate and has been previously described [20]. This linked dataset includes information on a variety of demographics and pregnancy characteristics found on the birth certificate paired with clinical detail from the delivery hospitalization for practically all inpatient deliveries and has been described in detail elsewhere [21]. For California vital records, the definition of stillbirth is a fetal death delivered at 20 weeks or more gestation. Stanford University Institutional Review Board and the California State Committee for the Protection of Human Subjects have reviewed and approved this study.

Study population

From 1991 to 2011, there were 11,559,616 deliveries in California. Inclusion criterion for the study was singleton live birth or stillbirth delivery (n = 11,234,886). Included were deliveries between 20 and 45 weeks gestational age based on last menstrual period (n = 10,674,900). Exclusion criteria were maternal age less than 13 or greater than 55 years or missing (0.01%) and paternal age less than 13 or greater than 70 years (0.01%) or missing (7%). After applying exclusion criteria, there were 9,931,407 deliveries included for analyses with 48,534 stillbirths (0.49%), where stillbirths are defined as in utero fetal deaths delivered at 20 or more weeks' gestation. All variables for study were extracted from the birth or fetal death certificate. Gestational age at delivery in weeks was assessed continuously in 1-week intervals. Maternal and paternal education were categorized as some high school or less, high school diploma or equivalent, some college, college graduate or more, or missing. Maternal and paternal race/ethnicity were categorized as non-Hispanic white, non-Hispanic black, Asian, Pacific Islander, Hispanic, American Indian/Alaskan Native, Other, or missing. Parity was categorized as nulliparous, multiparous, or missing. Maternal and paternal demographics are presented in Table 1.

Table 1
Demographics of the study population, California deliveries 1991–2011

Characteristic	Total, N = 9,931,407
Birth outcome, *n* (%)	
Live birth	9,882,873 (99.51)
Stillbirth	48,534 (0.49)
Maternal age (y), mean (SD)	27.9 (6.19)
Maternal race/ethnicity, *n* (%)	
Non-Hispanic white	3,260,703 (33.11)
Non-Hispanic black	565,191 (5.74)
Asian	1,132,600 (11.5)
Pacific Islander	51,713 (0.53)
Hispanic	4,790,338 (48.64)
American Indian/Alaskan Native	42,160 (0.43)
Other	6461 (0.07)
Missing	82,241
Maternal education, *n* (%)	
Some high school or less	2,790,660 (28.61)
High school diploma or equivalent	2,745,374 (28.14)
Some college	2,043,201 (20.95)
College graduate or more	2,175,275 (22.3)
Missing	176,897
Parity, *n* (%)	
Nulliparous	3,879,366 (39.08)
Multiparous	6,048,070 (60.92)
Missing	3971
Paternal age (y), mean (SD)	30.49 (7.11)
Paternal race/ethnicity, *n* (%)	
Non-Hispanic white	3,252,787 (33.07)
Non-Hispanic black	698,763 (7.1)
Asian	1,010,069 (10.27)
Pacific Islander	54,193 (0.55)
Hispanic	4,770,838 (48.51)
American Indian/Alaskan Native	41,566 (0.42)
Other	7529 (0.08)
Missing	95,662
Paternal education, *n* (%)	
Some high school or less	2,684,524 (27.99)
High school diploma or equivalent	2,912,554 (30.37)
Some college	1,783,369 (18.59)
College graduate or more	2,210,238 (23.05)
Missing	340,722

Statistical analysis

A Cox proportional hazard model with gestational age in completed weeks as the underlying time was used to estimate the relative rate of stillbirth defined as the hazard ratio (HR) and 95% confidence interval (CI) for maternal and paternal age in separate models. Given the shortest gestation recognized by California was 20 weeks for a live birth and stillbirth alike, time zero is set as 19 weeks. Live birth is considered as a competing event with the chance of being born dependent on parental age. As such, the results present the cause-specific hazard for stillbirth conditional on not being born before a given gestational age. Accordingly, HRs generated by the Cox model should be interpreted as risk ratios. HRs for stillbirth, according to maternal age, were compared with the population mean maternal age, 28 years, as the referent group. Maternal age was modeled as crude, maternally adjusted (education, race/ethnicity, and parity), and maternally and paternally (age, education, and race/ethnicity) adjusted. Education, race/ethnicity, and parity were identified as potential confounders of the relationship between parental age and stillbirth. Alternatively, HRs estimated for paternal age were compared with mean paternal age, 30 years, and were modeled as crude, paternally (education and race/ethnicity) adjusted, and paternally and maternally (age, education, race/ethnicity, and parity) adjusted. The proportional hazards assumption was evaluated using the Schoenfeld residuals, which revealed generally flat lines centered around 0 for all variables indicating their coefficients did not change appreciably over time. The cumulative incidence of stillbirth was also calculated conditional on reaching a given gestational week without being born.

Maternal and paternal ages were modeled separately using restricted cubic splines to allow for the nonlinear relationship with stillbirth. Knots were placed at the default percentiles as recommended by Harrell [22], between three and seven knots, and compared using model Akaike Information Criterion. Akaike Information Criterion values produced by each default knot placement were not substantially different. A 5-knot structure was ultimately chosen based on actual stillbirth rates by age that depicted similar inflection points (data not shown). Knots for maternal and paternal were placed at the 5th, 27.5th, 50th,

72.5th, and 95th percentiles of their distributions. For maternal age, this generated knots at ages 18, 24, 28, 32, and 38 years. Knots for paternal age were placed at 20, 26, 30, 34, and 43 years.

In the United States, mean maternal age has risen for all birth orders, but this increase has been more pronounced for age at first birth [1]. Analysis stratified on parity was performed to determine whether the overall association between parental age and stillbirth rate was considerably altered by a previous live birth to the mother.

Sensitivity analysis

The time variable gestational age at delivery in weeks on the California birth/fetal death certificate was updated from a last menstrual period estimate to the more accurate obstetric estimate in 2007. Three sensitivity analyses were conducted limiting to the period 2007–2011. The first sensitivity analysis, containing 2,381,183 deliveries, was a replication of the main results based on the aforementioned methods. This analysis contained two additional variables: maternal smoking during pregnancy (yes, no, and missing) and maternal prepregnancy body mass index (underweight, normal, overweight, obese I, obese II, obese III, and missing). Knot placement and referent group were based on the new age distributions, which did not vary substantially compared with 1991–2011. Next, a complete case analysis was performed where records with any missing covariate information were excluded. Lastly, a sensitivity analysis was performed on 2007–2011 data where multiple imputation was used to impute missing data for parity and parental age, education, and race/ethnicity. All dependent and independent variables used in adjusted analyses were used to impute missing values across five imputations.

All analyses were performed using SAS 9.4 (Cary, NC).

Results

In California, the average maternal and paternal ages were 28.8 and 31.1 years, respectively, in 2011. The increase in mean age for mothers and fathers from 1991 to 2011 was roughly the same, about 1.8 years. The correlation between maternal and paternal age was 0.74. Teenage mothers were more frequent than teenage fathers (9.3% vs. 4.2%), but the frequency of fathers ages 40 years and older was greater (10.5% vs. 3%; Table 2) than that of mothers. Most deliveries were to mothers aged 25–29 years (27.4%) and fathers aged 30–34 years (25.8%). The proportion of all deliveries that were stillbirth was 0.5% (Table 1). The distribution of gestational age among stillbirths was somewhat bimodal with two peaks around 21–23 weeks and 38–39 weeks (Fig. 1).

Table 2
Maternal and paternal age categories and birth outcomes

Characteristic	Live births	Stillbirths
	N (%)	*N* (%)
Maternal age (y)		
<20	925,339 (9.36)	4957 (10.21)
20–24	2,248,162 (22.75)	10,293 (21.21)
25–29	2,710,438 (27.43)	11,743 (24.20)
30–34	2,437,091 (24.66)	11,351 (23.39)
35–39	1,266,971 (12.82)	7494 (15.44)
40–44	280,145 (2.83)	2468 (5.09)
45–49	13,961 (0.14)	219 (0.45)
≥50	766 (0.01)	9 (0.02)
Paternal age (y)		
<20	417,061 (4.22)	2414 (4.97)
20–24	1,737,003 (17.58)	8620 (17.76)
25–29	2,467,853 (24.97)	11,301 (23.28)
30–34	2,550,434 (25.81)	11,428 (23.55)
35–39	1,676,298 (16.96)	8273 (17.05)
40–44	709,736 (7.18)	4181 (8.61)
45–49	229,409 (2.32)	1566 (3.23)
≥50	95,079 (0.96)	751 (1.55)

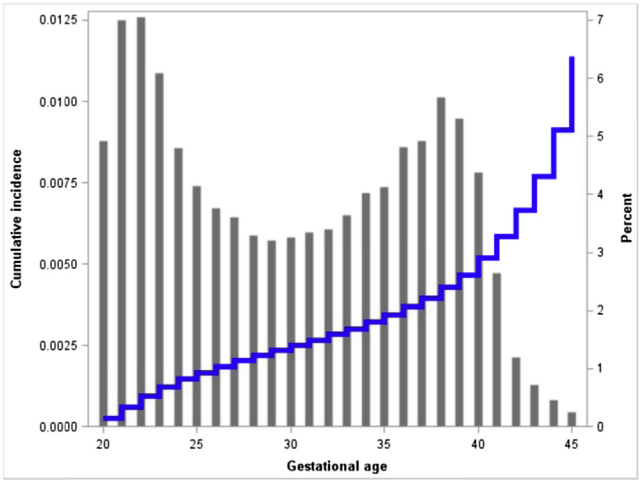

Fig. 1. Percent distribution (bars, right y-axis) and cumulative incidence (step, left y-axis) of stillbirth by gestational age.

Unadjusted curves for the relations between maternal and paternal ages and stillbirth were both J-shaped. However, HRs for older mothers and stillbirth increased more sharply than for older fathers (HR [95% CI]: 50-year-old mother: 4.44 (4.12–4.78); 50-year-old father 1.70 (1.63–1.77). The nadirs of the two curves were also slightly different (Figs. 2A and 3A). For mothers, 25-year-olds had the lowest HR for stillbirth relative to 28-year old mothers, whereas 29-year-old fathers experienced the lowest HR compared with 30-year-olds.

After adjusting for maternal education, race/ethnicity, and parity, young maternal age was no longer associated with an increased HR for stillbirth, but rather showed reduced HRs (Fig. 2B). This finding remained after entering paternal covariates into the model (Table 3). All maternal ages greater than the average had significantly increased HR for stillbirth ranging from 1.04 (1.03, 1.04) for 29-year-olds to 7.78 (7.00, 8.66) for 55-year-olds.

The HR observed for young paternal age and stillbirth was only slightly smaller in a model that adjusted for paternal education and race/ethnicity. With the addition of maternal covariates education, race/ethnicity, and parity, the HR for young paternal age remained elevated, whereas the HR at older age was lessened producing a more U-shaped curve (Fig. 3B). Fathers starting at age 39 years (HR [95% CI]: 1.04 [1.00–1.07]) had elevated HR for stillbirth all the way up to 70 years (HR [95% CI]: 1.68 [1.50–1.88]).

Models stratified on parity exhibited little influence on the results; that is, observed results for first-time mothers were essentially the same (Supplemental Fig. 1). The only noticeable difference was that young paternal age had greater HR for stillbirth among multiparous deliveries compared with nulliparous in models adjusted for both parental ages, education, and race (Supplemental Fig. 2).

Sensitivity analyses of data limited to 2007–2011 deliveries, accompanied by the obstetric estimate of gestation and covariates for maternal smoking during pregnancy and prepregnancy body mass index, did not alter the results (Supplemental Table 1). Likewise was the scenario after imputing missing data and combining parameter estimates across the five imputations.

Discussion

This population-based cohort of nearly 10 million California deliveries showed that after accounting for both parents' age,

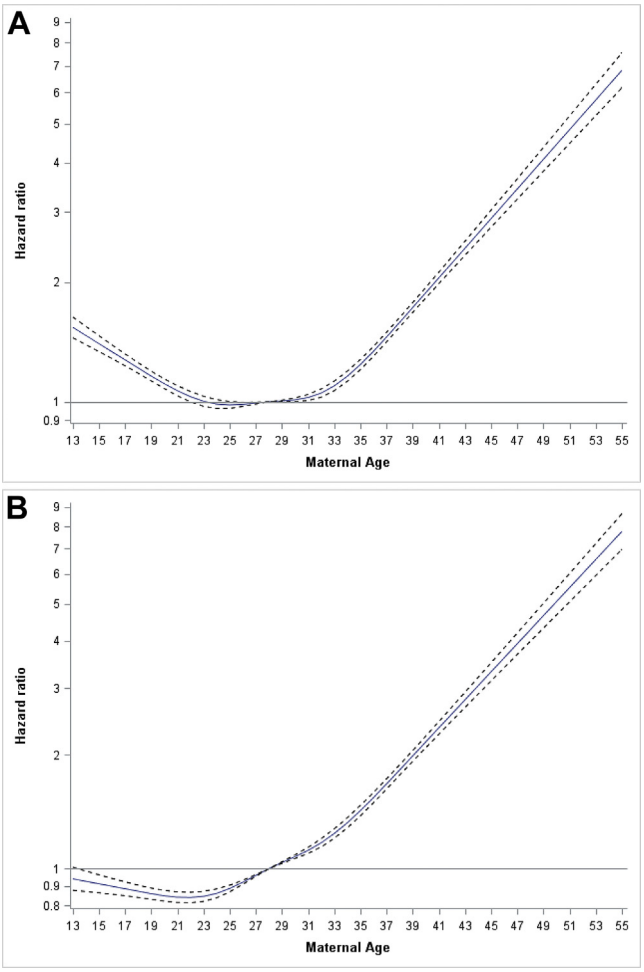

Fig. 2. (A) Unadjusted and (B) adjusted hazard ratio for stillbirth and maternal age, 1991–2011. Restricted cubic spline with five knots (maternal age: 18, 24, 28, 32, and 38 years); referent maternal age = 28 years; adjusted for maternal race/ethnicity, education, parity and paternal age, race/ethnicity, and education.

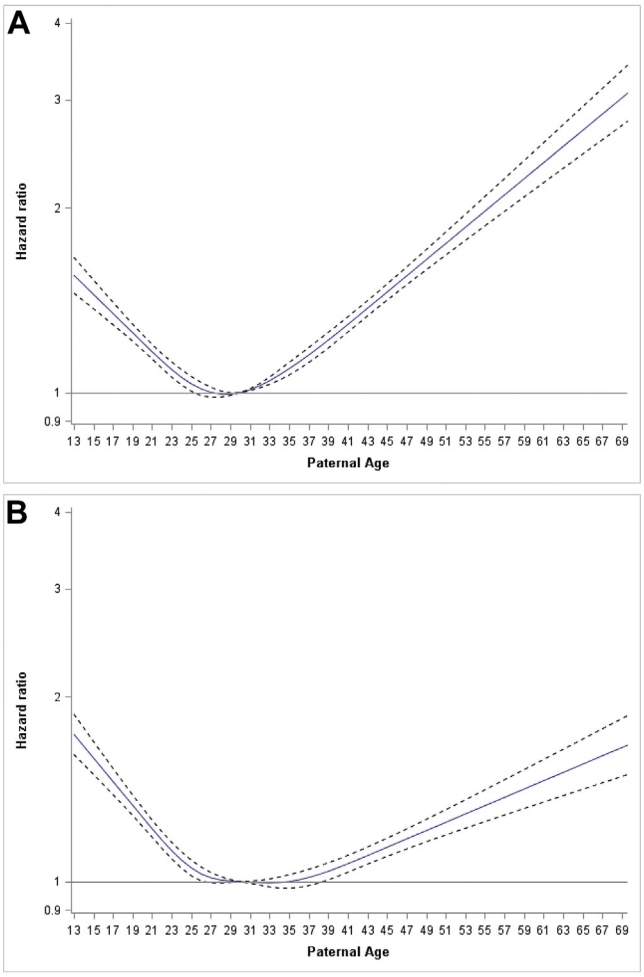

Fig. 3. (A) Unadjusted and (B) adjusted hazard ratio for stillbirth and paternal age, 1991–2011. Restricted cubic spline with five knots (paternal age: 20, 26, 30, 34, and 43 years); referent paternal age = 30 years; adjusted for paternal race/ethnicity, education, and maternal age, race/ethnicity, education, and parity.

education, race/ethnicity, and parity, older mothers (>28 years of mean age), and younger and older fathers (relative to mean age of 30 years) had increased rates of stillbirth deliveries. This work complements previous literature on the topic by presenting the stillbirth risk for maternal and paternal age from the same population.

The present results are in agreement with other population-based cohort studies that observed increased stillbirth risk among mothers aged 30 years and older [8,10,23]. Three systematic reviews, Huang et al. [24], Flenady et al. [25], and Lean et al. [4], also concluded that advanced maternal age poses an increased risk of stillbirth. Except for Schummers et al. [10], where they estimated absolute risk, maternal age was categorically modeled, thereby limiting the across study comparability of the magnitude of stillbirth risk. However, risks for the oldest mothers were the highest and ranged from 1.5- to 3-fold. Standard categorical variable analysis of maternal age creates a pooled estimate within a given group driven by its largest frequency. Stillbirth risks in the present study, where maternal age was modeled continuously, were slightly greater than two-fold for 40-year-olds but reached nearly eight-fold among 55-year-olds. Similar results were found when the analysis was stratified on parity. Waldenstrom et al. [6] found that advanced maternal age was only a risk factor for stillbirth among nulliparous mothers. They also present analysis showing a reduced association between advanced maternal age and stillbirth when limiting analyses to highly educated or nonsmoking, nonobese mothers. A separate study by Auger et al. also find that low education is an independent risk factor for stillbirth [26]. Our findings may differ with those from Waldenstrom et al. because they only

Table 3
Adjusted HRs for stillbirth and selected maternal and paternal ages, 1991–2011

Age (y)	Maternal*	Paternal†
	HR (95% CI)	HR (95% CI)
18	0.87 (0.84–0.90)	1.39 (1.33–1.45)
20	0.85 (0.82–0.88)	1.27 (1.23–1.32)
24	0.86 (0.84–0.88)	1.08 (1.05–1.12)
28	1.00 (reference)	1.01 (0.99–1.02)
30	1.08 (1.06–1.09)	1.00 (reference)
32	1.17 (1.14–1.20)	1.00 (0.99–1.00)
36	1.54 (1.49–1.59)	1.01 (0.98–1.04)
40	2.16 (2.09–2.24)	1.05 (1.02–1.09)
44	3.04 (2.89–3.20)	1.12 (1.08–1.16)
48	4.28 (3.99–4.59)	1.19 (1.15–1.24)
50	5.07 (4.68–5.50)	1.23 (1.18–1.29)

* Restricted cubic spline with five knots (maternal age: 18, 24, 28, 32, and 38 years); referent maternal age = 28 years; adjusted for maternal race/ethnicity, education, parity and paternal age, race/ethnicity, and education.

† Restricted cubic spline with five knots (paternal age: 20, 26, 30, 34, and 43 years); referent paternal age = 30 years; adjusted for paternal race/ethnicity, education, and maternal age, race/ethnicity, education, and parity.

included deliveries reaching 28 weeks and later. Of note, 58% of the stillbirths in the present study were 28 gestational weeks or more at delivery. Another study, Frederickson et al. [7], found limited support for advanced maternal age and increased stillbirth risk. The authors observed 35- to 39-year-olds had increased stillbirth risk but that mothers aged 40 years and older did not. The referent group in this study, however, was broad and likely contained considerably heterogeneity as it comprised 20- to 34-year-olds.

As observed in our unadjusted analysis of maternal age and stillbirth, previous studies have also shown increased stillbirth risk with young maternal age [27–29]. However, after we controlled for maternal and paternal sociodemographic covariates, young maternal age no longer showed increased risk, in fact, after adjustment appeared to reverse in its direction of risk. Similarly, a study of Swedish births by Olausson et al. [30] found that the association between young maternal age and late stillbirth was substantially reduced after adjusting for socioeconomic status. Another study by Jolly et al. [31] found that teenagers were not more likely to have a stillbirth compared with pregnant women aged 18–34 years. Teenage pregnancy may be characterized by low socioeconomic status and behavioral factors such as smoking and drug use, which are independent risk factors for stillbirth [32]. However, the biological association of low maternal age on stillbirth, independent of known behavioral risk factors, remains unclear. The causes of stillbirth vary by gestational age [33,34]. Whether the causes of stillbirth differ by maternal age is unknown. However, certain obstetric comorbidities that are associated with preterm delivery, such as hypertension and preeclampsia, are more common among older mothers and may impact the etiology behind certain types of stillbirths and placental abnormalities [35,36].

Our observed results of paternal age and stillbirth are in agreement with those of a recent population-based study from Denmark [13]. That is, fathers younger and older than the average age had increased stillbirth rates exhibiting a J-shaped pattern. Similar statistical approaches (e.g., splines, gestational age as underlying time, and livebirth as a competing event) were applied across the studies, which contribute to the robustness of the findings. The current results were able to extend those of the Danish study by controlling for two important independent risk factors for stillbirth, namely, maternal obesity and smoking, in a sensitivity analysis. Both Demark and California had similar rates of stillbirth, about 0.5%. On average, fathers were 2 years older in Denmark compared with California. The relationship between paternal age and stillbirth deserves attention as the rate of *de novo* mutations, decreased sperm quality, and certain birth defects have been associated with older fathers [16,17,37]. Elevated stillbirth rates were observed in the present analysis independent of maternal age, an important risk factor for some chromosomal abnormalities [38].

An important strength of this study was the nearly 10 million deliveries occurring over more than two decades. The generalizability of the findings is likely high considering about one in eight U.S. births is delivered in California. The simultaneous assessment of maternal and paternal ages from the same population-based cohort extends the literature on parental age and stillbirth. The robustness of the results across various sensitivity analysis should be highlighted. The findings were unchanged based on the estimation of gestational age, parity, period, multiple imputation, and the inclusion of maternal smoking, weight, and height data.

This study was not without limitation. Paternal age was missing in roughly 7% of records although the sensitivity analysis by statistically imputing missing paternal age did not change our conclusion. Multiple pregnancies to the same mother were present in the analysis. This was taken into account by performing analysis stratified on parity where nulliparous women could contribute only one pregnancy. It is important to note that in paternal age analysis where data were stratified on parity, information on first-time or not first-time fathers was not present. The minimum gestational age at which birth and fetal death certificates are recorded in California is 20 weeks. This means that the time window for inclusion into the study began after the time in which many early pregnancy losses occur. Terminations of pregnancy that include miscarriage and abortion are competing events that were unable to be accounted for. Moreover, we were limited to data available from administrative and vital records; thus, certain granular details about the parents or gestation were not available.

Nevertheless, our findings show that both older mothers and fathers have higher stillbirth rates. Parental age continues to rise in the United States, and the topic deserves attention owing to its association with reproductive outcomes such as stillbirth.

Acknowledgments

This project was supported by the March of Dimes Prematurity Research Center at Stanford University (MOD PR625253).

Research data: The data used for this study are administered by the Office of Statewide Health and Planning (OSHPD). OSHPD provides access to these data for research purposes but does not allow the data to be shared publicly to maintain confidentiality and privacy. Researchers who wish to access these data may submit a data request directly to OSHPD.

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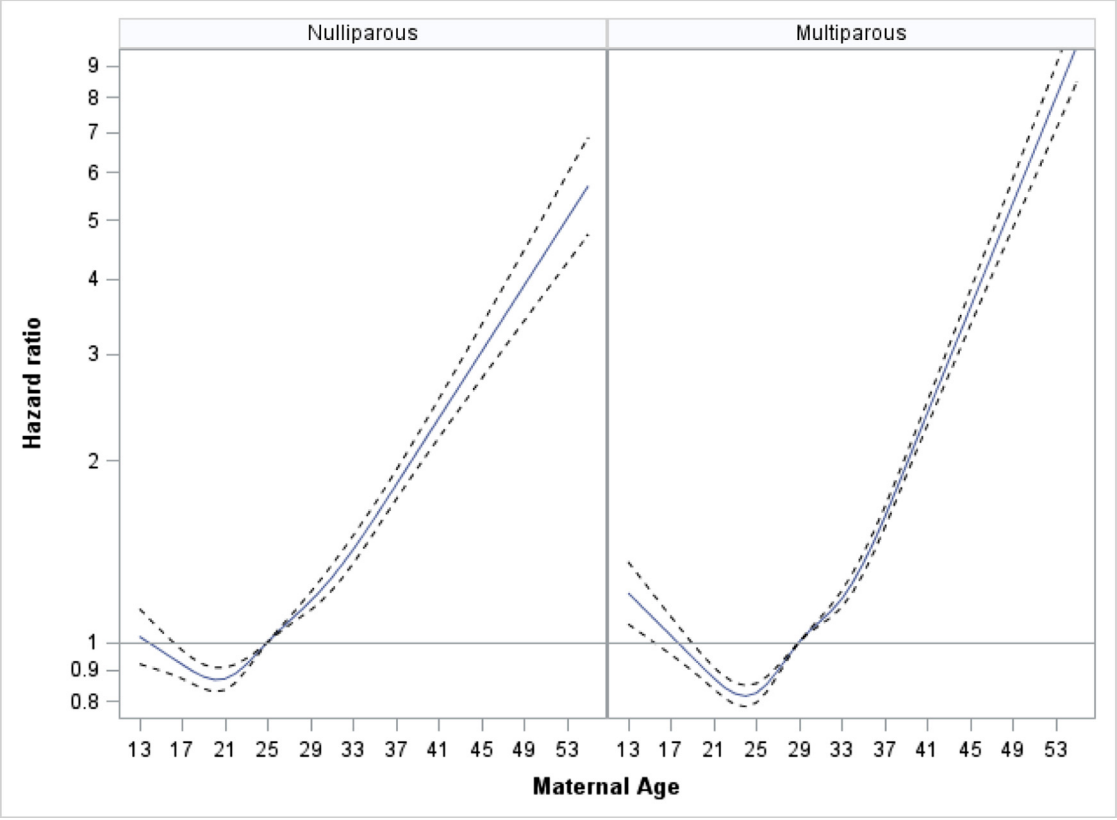
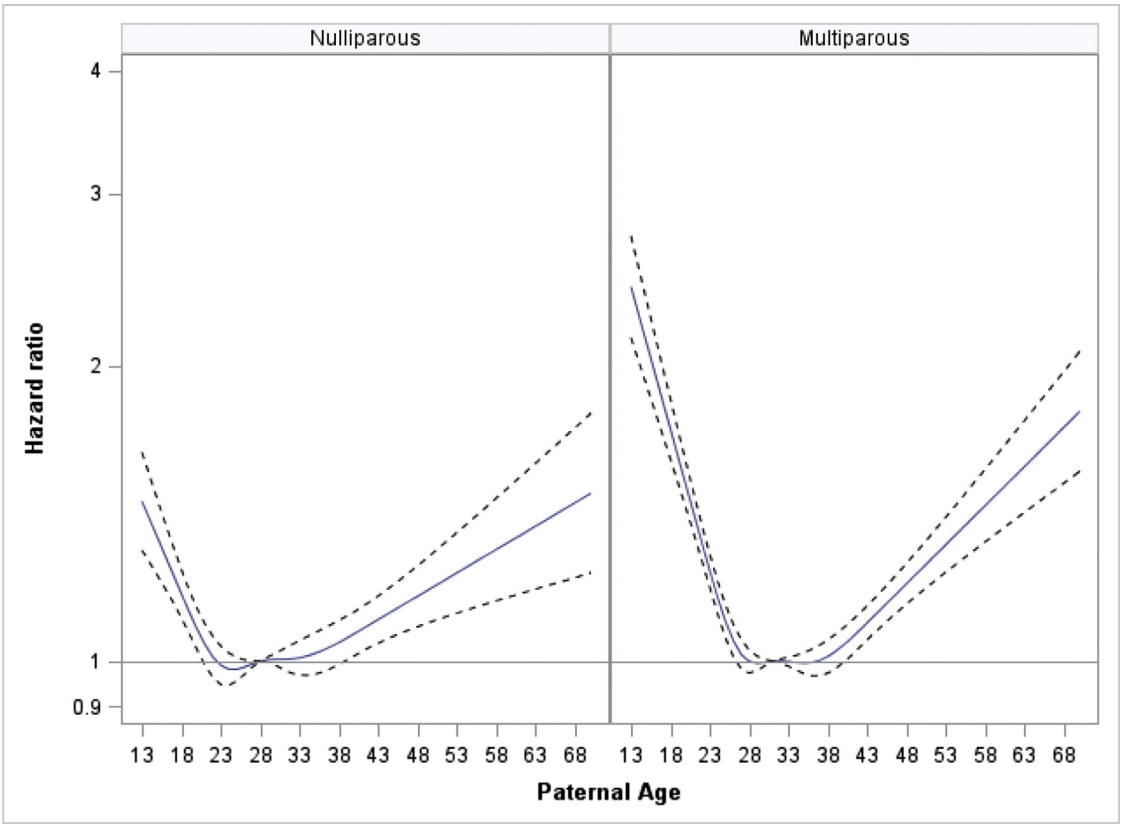
Appendix



Supplemental Fig. 1. Adjusted hazard ratio for stillbirth and maternal age stratified on parity, 1991–2011. Restricted cubic spline with five knots (maternal age, nulliparous: 17, 21, 25, 30, and 37 years; multiparous: 20, 25, 29, 33, and 39 years); referent maternal age (nulliparous = 25 years; multiparous = 29 years); adjusted for maternal race/ethnicity, education, and paternal age, race/ethnicity, and education.



Supplemental Fig. 2. Adjusted hazard ratio for stillbirth and paternal age stratified on parity, 1991–2011. Restricted cubic spline with five knots (paternal age, nulliparous: 18, 23, 28, 32, and 41 years; multiparous: 22, 27, 31, 36, and 43 years); referent paternal age (nulliparous = 28 years; multiparous = 31 years); adjusted for paternal race/ethnicity, education, and maternal age, race/ethnicity, and education.

Supplemental Table 1
Adjusted hazard ratios for stillbirth and selected maternal and paternal ages, 2007–2011*

Age	Maternal†	Paternal‡
	HR (95% CI)	
18	0.97 (0.90–1.05)	1.49 (1.36–1.64)
20	0.92 (0.86–0.99)	1.36 (1.27–1.46)
24	0.89 (0.84–0.95)	1.14 (1.07–1.21)
28	1.00 (reference)	1.02 (1.00–1.05)
32	1.07 (1.02–1.12)	0.98 (0.97–1.00)
36	1.35 (1.27–1.45)	0.98 (0.93–1.03)
40	1.93 (1.80–2.08)	1.02 (0.95–1.09)
44	2.79 (2.52–3.09)	1.09 (1.01–1.16)
48	4.03 (3.50–4.65)	1.16 (1.07–1.26)
50	4.85 (4.12–5.71)	1.20 (1.10–1.32)

* Gestational age at delivery based on obstetric estimate.
† Restricted cubic spline with five knots (maternal age: 19, 24, 28, 32, and 39 years); referent maternal age = 28 years; adjusted for maternal race/ethnicity, education, parity, pre-pregnancy BMI, smoking during pregnancy and paternal age, race/ethnicity, and education.
‡ Restricted cubic spline with five knots (paternal age: 20, 26, 31, 35, and 44 years); referent paternal age = 31 years; adjusted for paternal race/ethnicity, education, and maternal age, race/ethnicity, education, parity, pre-pregnancy BMI, and smoking during pregnancy.