Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study

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ABSTRACT

OBJECTIVE
To evaluate the impact of advanced paternal age on maternal and perinatal outcomes in the United States.

DESIGN
Retrospective, population based cohort study.

SETTING
US.

POPULATION

MAIN OUTCOME MEASURES
Primary perinatal outcomes were gestational age, birth weight, Apgar score at five minutes, admission to a neonatal intensive care unit, need for postpartum antibiotics, and seizures. Primary maternal outcomes were gestational diabetes and pre-eclampsia. Secondary outcome was the number of preventable perinatal events.

RESULTS
Higher paternal age was associated with an increased risk of premature birth, low birth weight, and low Apgar score. After adjustment for maternal age, infants born to fathers aged 45 years or older had 14% higher odds of premature birth (odds ratio 1.14, 95% confidence interval 1.13 to 1.15), independent of gestational age, and 18% higher odds of seizures (1.18, 0.97 to 1.44) compared with infants of fathers aged 25 to 34 years. The odds of gestational diabetes was 34% higher (1.34, 1.29 to 1.38) in mothers with the oldest partners. 13.2% (95% confidence interval 12.5% to 13.9%) of premature births and 18.2% (17.5% to 18.9%) of gestational diabetes in births associated with older fathers were estimated to be attributable to advanced paternal age.

CONCLUSIONS
Advanced paternal age is associated with negative effects on both mothers and offspring. Given the relatively low prevalence of advanced paternal age in the US, population level impacts are currently modest. Nevertheless, as advanced paternal age has doubled in the US over the past generation, further investigation is warranted of the impact on birth outcomes and public health.

Introduction
The age at which couples have children in the United States continues to increase.1,2 The number of first births to women older than 35 years has risen by about 2% annually since the 1970s, and the percentage of all births in the US to fathers aged more than 40 has doubled, to 9%, over the same period. Though the effects of advanced maternal age on perinatal outcomes have been extensively studied, research on the impact of older fathers on the health of offspring has been limited mostly to the risk of congenital disease.3-8

The high number of male germ cell divisions in aging fathers has been proposed to increase the risk of autism, genetic abnormalities, psychiatric morbidity, and neoplasia in offspring, but recent studies have also suggested a potential paternal effect on perinatal morbidity.6,9-14 One common explanation arises from the epigenetic changes that occur within spermatocytes; specifically modifications to histone and DNA methylation in spermatozoa of older men. These alterations occur in regions of the genome that are responsible for several diseases in offspring.15 Disruption of histone methylation in developing male germ cells might be a precursor to aberrant embryonic and placental development, with studies suggesting that paternal imprinting of aging could affect both fetal growth and maternal health during pregnancy.16,17

Utilizing birth registries, several groups have attempted to characterize the risk of advanced paternal age on adverse birth events such as preterm birth, low birth weight, and pre-eclampsia.18 Findings remain inconclusive, however, owing to insufficient sample sizes, short study periods, and difficulty obtaining reliable data on paternal age.18,20 Thus, the potential association between advanced...
paternal age and health of the mother and offspring remains poorly defined. We examined the association of paternal age on maternal and neonatal health and estimated the impact of advancing paternal age in the US.

Methods

Data source
In this retrospective cohort analysis, we drew on data published by the National Vital Statistics System, a federal data sharing programme provided by the Centers for Disease Control and Prevention and the National Center for Health Statistics. Through contracts with individual vital registration systems within each state, the National Center for Health Statistics compiles data on live births from birth certificates and permits distribution of these statistics for medical research purposes. Standard birth certificates contain self reported parental demographics such as age, race, and education as well as pregnancy and birth outcomes, which are documented by healthcare providers. All births occurring within the US since 1985 are captured by this system.\(^2\) 21 The National Center for Health Statistics provides training modules and guidelines for healthcare practitioners collecting birth data to ensure completion, accuracy, and standardization for reporting of vital events.\(^22\) Coding of the data also undergoes rigorous statistical quality checks and is edited for accuracy by the National Center for Health Statistics. If systematic reporting failures are noted, records are returned to the registration site for correction.\(^20\)

Study cohort and demographic variables
In our analysis, we included all reported live births between 2007 and 2016 within the US. We compiled data files sequentially by year and extracted all available demographic variables, including age, race, education, marital status, smoking history, and access to care. Paternal age was categorized into 10 year intervals: <25, 25-34, 35-44, 45-54, and 55 or older.\(^23\) Five year intervals were also analyzed, though no significant difference in trends were noted (see supplemental table 1). Racial categories were defined by the US Office of Management and Budget, and we categorized participants on the basis of how they self identified. Data on paternal education were unavailable until 2009 owing to the collection policy of the National Center for Health Statistics. We used inverse probability weighting to account for missing paternal data from birth certificates.\(^2\) 24 To account for inconsistent reporting of paternal data across various demographics, we utilized a logistic regression model incorporating maternal age, race, birth year, and education to model the probability of paternal reporting for each birth. Inverse probability weighting was subsequently applied to all statistical analyses to maximize generalizability to all births. This weighting methodology has been described previously.\(^26\)

Outcomes
The primary outcome of interest was the perinatal risk to child and mother correlated with advanced paternal age. We conducted a preliminary literature search to determine birth outcomes that have previously been associated with advanced paternal ages. Of these variables, we subsequently included those available within the National Vital Statistics System data files. Neonatal outcomes evaluated were premature birth (gestational age <37 weeks), low birth weight (<2500 g), low five minute Apgar score (<8), assisted ventilation at birth, admission to the neonatal intensive care unit, requirement for postpartum antibiotics, and seizures.\(^25\) 26 We defined a neonatal adverse event as the requirement or occurrence of at least one of: assisted ventilation, admission to the neonatal intensive care unit, antibiotics, or seizure. The maternal outcomes evaluated were gestational diabetes, pre-eclampsia, and eclampsia. All variables were categorized as dichotomous, with gestational age, birth weight, and Apgar score also presented as continuous variables. For each paternal age group, we also evaluated the sex ratio of all births.

Statistical analysis
We analyzed mean paternal age with standard deviations along with standard demographics of all live births from 2007 and 2016 as a pooled cohort. To estimate the adjusted odds ratio for each perinatal outcome by paternal age group, we created logistic regression models with fathers aged 25 to 34 years as the reference group. Given the collinearity between paternal and maternal age, we also carried out stratified analyses based on maternal age and sensitivity analyses. Moreover, given the association between adverse birth outcomes and prematurity, we conducted separate analyses with only full term infants (see supplemental table 2). Other subgroup analyses were done to ensure that the paternal age association was not confounded by paternal age grouping, birth order, birth year, or missing paternal data (see supplemental tables). To test for a systematic change in sex ratio between paternal age groups, we compared the number and percentage of male and female births to each paternal age group. We used the Wilcoxon rank-sum test to determine statistically significant differences among age groups. A regression analysis was also conducted for each paternal age group to determine adjusted odds ratios of having a son.

The number and percentage of men who fathered children with each morbidity were compared. We also estimated the number of preventable perinatal events if fathers within the US were all younger than 45 years. The population attributable risk was calculated using the standard formula (observed prevalence–predicted prevalence of outcome after shift to new distribution of younger fathers)/(observed prevalence).\(^27\) 28 All statistical analysis was carried out using Stata version 14 (College Station, TX) and the user written package punaf (population attributable risk fraction).\(^29\) Statistical tests were two sided and 99 per cent
confidence intervals were provided for precision of the estimates.

**Patient and public involvement**

The public was not involved in the development of the research question, formation of the study design, analysis of data, or interpretation of results. There are no plans to directly disseminate the study results to the study participants or wider patient communities.

**Results**

A total of 40529905 live births between 2007 and 2016 in the United States were evaluated. Table 1 shows paternal, maternal, and infant characteristics. The mean age of fathers during this period increased from 30.0 years to 31.2 years.

After adjustment for maternal age, race, education, smoking status, and number of prenatal visits, births related to the oldest fathers were associated with

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**Table 1** Paternal, maternal, and infant characteristics by paternal age group. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Paternal age (years)</th>
<th>&lt;25</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>≥55</th>
<th>Missing paternal age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth certificates</td>
<td></td>
<td>6 319 860 (15.6)</td>
<td>18 289 776 (45.1)</td>
<td>8 476 310 (20.9)</td>
<td>1 091 848 (2.7)</td>
<td>1 111 130 (0.3)</td>
<td>6 240 981</td>
</tr>
</tbody>
</table>

**Paternal characteristics**

- **Race:**
  - White: 2 675 449 (42.3)
  - Black: 1 173 282 (18.6)
  - Native American: 84 260 (1.3)
  - Asian: 86 488 (1.4)
  - Hispanic: 2 046 130 (32.4)
  - Other or unknown: 254 251 (4.0)

- **Mean (99% CI) birth weight (g):**
  - 3220 (3194 to 3226.0)
  - 3006.6 (3003.6 to 3036.9)
  - 3046 (3041.1 to 3050.2)
  - 3253.2 (3251.6 to 3254.8)
  - 3204 (3197.4 to 3207.4)

- **Median (interquartile range):**
  - No of prenatal visits: 11 (9-13)

- **Married:**
  - 2 108 222 (33.4)

- **Gestational diabetes:**
  - 185 717 (2.9)

- **Pre-eclampsia:**
  - 297 358 (4.7)

- **Eclampsia:**
  - 16 938 (0.3)

- **Infant characteristics**
  - Mean (99% CI) birth weight (g): 3200 (3194.4 to 3220.6)
  - Mean (99% CI) gestational age (weeks): 38.69 (38.68 to 38.69)
  - Premature birth (<37 weeks): 745 615 (11.8)
  - Low birth weight (<2500 g): 518 957 (8.2)
  - Low 5 minute Apgar score (<8): 258 283 (4.1)
  - Assisted ventilation: 200 197 (3.2)
  - Admission to NICU: 385 777 (6.1)
  - Postpartum antibiotics: 116 128 (1.8)
  - Seizures: 1 715 (0.0)
  - Adverse event: 524 725 (8.3)

**NICU = neonatal intensive care unit.**

**Missing paternal age data are presented as number of birth certificates without paternal age for each category and percentage of total number of missing paternal age data.**

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Table 2 | Multivariate linear regression models predicting effect of paternal age on birth outcomes before and after adjustment for year, maternal age, race, and education, and parental race and education, prenatal visits, tobacco use, and marital status. Values are linear regression coefficients or logistic regression odds ratios with 99% confidence intervals

<table>
<thead>
<tr>
<th>Birth outcomes</th>
<th>Paternal age (years)</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>≥55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age coefficient (weeks):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-0.03 (−0.04 to −0.03)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>-0.01 (−0.02 to −0.01)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight coefficient (g):</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Unadjusted</td>
<td>-86.6 (−87.3 to −85.9)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>-22.9 (−24.1 to −21.7)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apgar coefficient (5 min):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-0.03 (−0.04 to −0.03)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
<td>-0.02 (−0.02 to −0.02)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature birth (&lt;37 weeks):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.15 (1.15 to 1.16)</td>
<td>Reference</td>
<td>1.14 (1.14 to 1.15)</td>
<td>1.42 (1.41 to 1.43)</td>
<td>1.65 (1.62 to 1.69)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.03 (1.02 to 1.04)</td>
<td>Reference</td>
<td>1.06 (1.05 to 1.06)</td>
<td>1.14 (1.13 to 1.15)</td>
<td>1.25 (1.22 to 1.29)</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.20 (1.19 to 1.20)</td>
<td>Reference</td>
<td>1.14 (1.13 to 1.14)</td>
<td>1.46 (1.45 to 1.47)</td>
<td>1.78 (1.73 to 1.82)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.05 (1.04 to 1.06)</td>
<td>Reference</td>
<td>1.04 (1.04 to 1.05)</td>
<td>1.14 (1.12 to 1.15)</td>
<td>1.27 (1.22 to 1.31)</td>
</tr>
<tr>
<td>Low 5 minute Apgar score (&lt;8):</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.23 (1.23 to 1.24)</td>
<td>Reference</td>
<td>0.98 (0.97 to 0.98)</td>
<td>1.15 (1.14 to 1.17)</td>
<td>1.34 (1.29 to 1.39)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.11 (1.10 to 1.12)</td>
<td>Reference</td>
<td>0.97 (0.96 to 0.98)</td>
<td>1.04 (1.02 to 1.06)</td>
<td>1.14 (1.08 to 1.20)</td>
</tr>
<tr>
<td>Assisted ventilation:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.06 (1.05 to 1.07)</td>
<td>Reference</td>
<td>1.02 (1.02 to 1.03)</td>
<td>1.17 (1.15 to 1.18)</td>
<td>1.27 (1.21 to 1.32)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.04 (1.02 to 1.05)</td>
<td>Reference</td>
<td>1.00 (0.99 to 1.01)</td>
<td>1.06 (1.04 to 1.16)</td>
<td>1.10 (1.04 to 1.16)</td>
</tr>
<tr>
<td>Admission to NICU:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.03 (1.03 to 1.04)</td>
<td>Reference</td>
<td>1.12 (1.11 to 1.12)</td>
<td>1.39 (1.38 to 1.40)</td>
<td>1.64 (1.59 to 1.68)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.01 (1.00 to 1.02)</td>
<td>Reference</td>
<td>1.03 (1.03 to 1.04)</td>
<td>1.14 (1.13 to 1.16)</td>
<td>1.28 (1.24 to 1.33)</td>
</tr>
<tr>
<td>Postpartum antibiotics:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.13 (1.12 to 1.14)</td>
<td>Reference</td>
<td>0.96 (0.95 to 0.97)</td>
<td>1.09 (1.07 to 1.11)</td>
<td>1.20 (1.13 to 1.26)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.04 (1.03 to 1.06)</td>
<td>Reference</td>
<td>0.96 (0.95 to 0.97)</td>
<td>1.03 (1.00 to 1.05)</td>
<td>1.06 (0.99 to 1.14)</td>
</tr>
<tr>
<td>Seizures:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.14 (1.06 to 1.22)</td>
<td>Reference</td>
<td>0.98 (0.91 to 1.05)</td>
<td>1.13 (0.97 to 1.32)</td>
<td>1.21 (0.77 to 1.89)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.06 (0.93 to 1.20)</td>
<td>Reference</td>
<td>1.00 (0.91 to 1.11)</td>
<td>1.18 (0.97 to 1.44)</td>
<td>1.30 (0.77 to 2.20)</td>
</tr>
<tr>
<td>Adverse event*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.05 (1.05 to 1.06)</td>
<td>Reference</td>
<td>1.08 (1.07 to 1.08)</td>
<td>1.31 (1.30 to 1.32)</td>
<td>1.52 (1.48 to 1.55)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.03 (1.02 to 1.03)</td>
<td>Reference</td>
<td>1.02 (1.01 to 1.02)</td>
<td>1.12 (1.11 to 1.13)</td>
<td>1.24 (1.20 to 1.28)</td>
</tr>
<tr>
<td>Gestational diabetes:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.83 (0.82 to 0.83)</td>
<td>Reference</td>
<td>1.15 (1.15 to 1.16)</td>
<td>1.28 (1.27 to 1.29)</td>
<td>1.34 (1.30 to 1.38)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>0.82 (0.81 to 0.83)</td>
<td>Reference</td>
<td>1.16 (1.15 to 1.16)</td>
<td>1.28 (1.27 to 1.30)</td>
<td>1.34 (1.29 to 1.38)</td>
</tr>
<tr>
<td>Pre-eclampsia:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.04 (1.03 to 1.04)</td>
<td>Reference</td>
<td>1.00 (0.99 to 1.00)</td>
<td>1.11 (1.10 to 1.12)</td>
<td>1.15 (1.11 to 1.19)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.06 (1.05 to 1.07)</td>
<td>Reference</td>
<td>0.97 (0.96 to 0.97)</td>
<td>0.99 (0.98 to 1.01)</td>
<td>1.00 (0.96 to 1.05)</td>
</tr>
<tr>
<td>Eclampsia:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.21 (1.18 to 1.24)</td>
<td>Reference</td>
<td>1.06 (1.04 to 1.09)</td>
<td>1.25 (1.20 to 1.32)</td>
<td>1.34 (1.16 to 1.54)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>1.11 (1.06 to 1.16)</td>
<td>Reference</td>
<td>0.99 (0.96 to 1.03)</td>
<td>1.02 (0.95 to 1.10)</td>
<td>1.03 (0.84 to 1.25)</td>
</tr>
</tbody>
</table>

NICU = neonatal intensive care unit.
*Required assisted ventilation, admission to a NICU, postpartum antibiotics, or had seizure after birth.

worse outcomes (table 2). Gestational ages were lower in children born to fathers aged more than 45 years (on average 0.12 weeks younger, 99% confidence interval -0.13 to -0.11 weeks) and had 14% higher odds of having a premature birth (<37 weeks) compared with younger fathers (adjusted odds ratio 1.14, 99% confidence interval 1.13 to 1.15). Infants born to fathers aged 45-54 years were also born 20.2 g lighter (99% confidence interval -22.5 to -18.0) and had a 14% greater risk of low birth weight (<2500 g) than infants born to younger fathers (adjusted odds ratio 1.14, 99% confidence interval 1.12 to 1.15). The odds of having a low Apgar score (<8) was greater for fathers aged 55 years or older (1.14, 1.08 to 1.20).

Infants born to fathers aged 55 years or older also had a significantly higher risk of requiring additional medical care after birth. The odds of the infant requiring assisted ventilation increased by 10% (adjusted odds ratio 1.10, 99% confidence interval 1.04 to 1.16) and the odds of requiring admission to the neonatal intensive care unit increased by 28% (1.28, 1.24 to 1.33). The secondary sex ratio declined with increasing paternal age (table 3). Younger fathers (<25 years) were more likely to have a boy than fathers aged 25-34 years after adjustment for other paternal and maternal characteristics, including maternal age (adjusted odds ratio 1.01, 99% confidence interval 1.00 to 1.01). However, no change in the secondary sex ratio was
Table 3 | Comparison of sex ratio by paternal age group

<table>
<thead>
<tr>
<th>Paternal age (years)</th>
<th>&lt;25</th>
<th>25-34</th>
<th>35-44</th>
<th>45-54</th>
<th>≥55</th>
</tr>
</thead>
<tbody>
<tr>
<td>No (%) women</td>
<td>4134050 (48.7)</td>
<td>10351338 (48.8)</td>
<td>4612303 (48.8)</td>
<td>603896 (48.9)</td>
<td>60795 (48.8)</td>
</tr>
<tr>
<td>No (%) men</td>
<td>4361018 (51.3)</td>
<td>10870121 (51.2)</td>
<td>4835218 (51.2)</td>
<td>632267 (51.1)</td>
<td>64848 (51.2)</td>
</tr>
<tr>
<td>Odds ratio (99% CI)</td>
<td>1.01 (1.00 to 1.01)</td>
<td>Reference</td>
<td>1.00 (0.99 to 1.00)</td>
<td>1.00 (0.99 to 1.00)</td>
<td>1.00 (0.99 to 1.02)</td>
</tr>
</tbody>
</table>

Noted for fathers aged 45-54 years (1.00, 0.99 to 1.00). A subanalysis was additionally conducted excluding births that resulted from in vitro fertilization (1.53% of all births), with no changes to the conclusions.

Pregnancy-related outcomes for mothers were also examined. Fathers older than 45 years had a 28% increased odds of a pregnancy complicated by gestational diabetes compared with fathers in the reference group (1.28, 1.27 to 1.30), though no significant association was found between paternal age and risk of pre-eclampsia or eclampsia (0.99, 0.98 to 1.01 and 1.02, 0.95 to 1.10, respectively).

After stratification by maternal age, increasing paternal age remained significantly associated with perinatal outcomes, with similar trends across all strata for maternal age (fig 1 and supplemental table 3). In addition, similar findings were identified during separate periods (2007 v 2016) indicating that these trends were not influenced by recent changes in medical practice (see supplemental table 4).

To estimate the population attributable risk of advanced paternal age, we recalculated the distribution of paternal age groups for a scenario in which all fathers were younger than 45 years. Table 4 shows that over the past decade 13.2% (95% confidence interval 12.5% to 13.9%) of premature births and 14.5% (13.6% to 15.4%) of low birth weight infants with older fathers (under the assumption of a causal relation) can be attributed to the increase in number of fathers older than 45 years. Further, 15.1% (14.2% to 15.9%) of admissions to a neonatal intensive care unit and 18.2% (17.5% to 18.9%) of gestational diabetes diagnoses were also attributable to these older fathers.

Discussion

Paternal age is increasing in the United States with potential implications for maternal and child health. Infants born to fathers aged more than 35 years were found to be at a higher risk of premature birth, low birth weight, and increased morbidity (eg, assisted ventilation, stay in a neonatal intensive care unit, postpartum antibiotics) during the perinatal period. A large percentage of cases of premature births, low birth weight, and admissions to a neonatal intensive care unit in children of older fathers was found to be associated with advanced paternal age. In addition, increased paternal age was negatively associated with maternal health as identified through an increased risk of gestational diabetes. Though, as the prevalence of advanced paternal age was modest, the impact of these associations at a population level remains uncertain.

Indeed, the increased odds ratios were <1.5, suggesting the overall risk of these outcomes likely still remains low. The increased risks associated with father’s age appeared to be dose dependent, with a J-shaped association curve. While the youngest fathers tended to have worse perinatal outcomes than men in their 20s, fathers aged 45 years or older seemed to have significantly worse outcomes. This trend continued with increasing age (dose).

Comparison with other studies

The initial identification of paternal contribution to birth outcome dates back to Wilhelm Weinberg’s discovery in 1912 of a correlation between achondroplasia and...
Table 4 | Total number of affected births (weighted) and births attributable to paternal age 45 years and older for all perinatal outcomes. Values are percentages (unless stated otherwise) of total births.

<table>
<thead>
<tr>
<th>Perinatal outcomes</th>
<th>Total No of cases</th>
<th>Paternal age (years)</th>
<th>P value</th>
<th>% of cases prevented if paternal age was ≤45 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premature birth (&lt;37 weeks)</td>
<td>4,608,250</td>
<td>≤45 (11.3)</td>
<td>198,597 (14.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low birth weight (&lt;2500 g)</td>
<td>3,141,068</td>
<td>≤45 (7.7)</td>
<td>137,802 (10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low 5 minute Apgar score (≤8)</td>
<td>1,629,302</td>
<td>≤45 (4.0)</td>
<td>60,795 (4.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>2,225,092</td>
<td>≤45 (5.3)</td>
<td>129,696 (9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>1,876,535</td>
<td>≤45 (5.1)</td>
<td>68,901 (5.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>97,069</td>
<td>≤45 (0.2)</td>
<td>38,50 (0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Assisted ventilation</td>
<td>1,483,395</td>
<td>≤45 (3.6)</td>
<td>56,742 (4.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>3,035,690</td>
<td>≤45 (7.4)</td>
<td>133,749 (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postpartum antibiotics</td>
<td>816,272</td>
<td>≤45 (2.0)</td>
<td>29,992 (2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Seizures</td>
<td>11,794</td>
<td>≤45 (0.0)</td>
<td>44,6 (0.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Adverse event</td>
<td>3,351,823</td>
<td>≤45 (8.2)</td>
<td>141,815 (10.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NICU=neonatal intensive care unit.

birth order, but it was James Crow’s seminal work at
the turn of the century that spurred major interest into
paternal age effects on infant health.7 30 Still, there is a
dearth of published data on the paternal effects on
birth outcomes, and the little existing data have been
mostly equivocal. Studies evaluating the association
between paternal age and risk of pre-eclampsia, low Apgar scores, and admission to a neonatal intensive care
unit have also been rare.

One study evaluated 1.5 million births in Italy
between 1990 and 1998 and observed that fathers
aged 45 to 49 had a higher risk of severely preterm
births (<32 weeks of gestation) compared with fathers
aged 25 to 29, particularly in firstborn children.19

In contrast, a study of 2.5 million births in the US to
nulliparous women between 1995 and 2000 found
an association between teenage fathers and preterm
births but no association for fathers with advanced
age.20 In this study, however, only 0.5% of births
(13,907 total births) were to fathers aged more than
45. The risk of other perinatal complications, such as
pre-eclampsia, low birth weight, and low Apgar
scores also remains uncertain given mixed findings
from mostly underpowered studies.1 18 25 26 31-38 While
a study initially found that fathers older than 35 years
were at increased risk of low birthweight offspring,
the findings were later questioned owing to missing
paternal age thought to result in selection bias.20 33

Moreover, another study examined more than one
million births in Ohio from 2006 to 2012 and did not
identify associations between paternal age and pre-
eclampsia, preterm birth, fetal growth restriction,
genetic disorder, or admission to a neonatal intensive care unit.39

Recent studies have begun to uncover a potential
epigene tic link between the aging paternal genome
and health outcomes in offspring.40 Age dependent
alterations, such as DNA methylation, have been
observed in mammalian somatic and germline cells.
Higher rates of methylation were found on ribosomal
DNA of older rat spermatozoa compared with younger
controls.41 Additionally, genomic imprinting has been
suggested to influence placental growth, morphology,
and nutrient transfer, which in part explains the
paternal influence on birth outcomes.42 For example,
the overexpression of a demethylase enzyme (Kdm1a)
in mice was found to result in loss of methylation
of H3K4, an epigenetic marker associated with
developmental genes in sperm. The offspring of these
mice had increased rates of birth defects and neonatal
mortality.43 44 Similarly, interferon-like growth
factor 2 is a paternally expressed gene susceptible to
epigene tic modification that affects growth factors
for both the placenta and the embryo.16 17 This could
partially explain the increased placental weight found
in pregnancies to older fathers, which in turn has been
associated with an increased risk for pre-eclampsia
and other maternal comorbidities (eg, gestational
diabetes).45 It has become increasingly clear that male
aging influences germline integrity through other
mechanisms as well, such as DNA fragmentation,
telomere lengthening, mutations, and overall genomic
instability.23 Investigators have estimated that males
develop approximately two additional mutations in
their germline DNA throughout life, with de
ovo mutations increasing the risk of preterm birth.11 46
In addition, pre-eclampsia and epilepsy have also
been associated with paternal age.32 47 A need exists to
further elucidate the potential causal relation between
advanced paternal age and maternal and infant
outcomes, though it seems that the paternal effect
on placental health may play a non-trivial, though
speculative role.

Strengths and limitations of this study
The current study incorporates all live births over a
span of 10 years, allowing for an unbiased analysis
of recent trends. The pooling of all births during
this period minimizes the risk of confounding from
yearly fluctuations in perinatal outcomes. Moreover,
similar measures of association were identified from
separate periods within the cohort, indicating that
findings do not reflect a time dependent phenomenon.

Given the increased risk of negative birth outcomes
in premature births, a subset analysis with only term
births was conducted to corroborate the paternal
age findings. The addition of inverse probability
weighting further reduces the overrepresentation of
certain demographics of fathers: mostly older, college educated fathers who are more likely to be present at birth.\(^2\) Other advantages of utilizing national birth certificate data provided by the National Center for Health Statistics are that this unique system allows for incorporation of important covariates as well as for the formulation of weighting to adjust for missing paternal data. The inclusion of all births within the US allows for estimation of rates of occurrence and associated attributable risk fractions, which facilitates evaluation of the public health impact of aging fathers.\(^29\)

Though this study found an overall positive association between older fathers and declining sex ratio, the oldest group still maintained a similar proportion of male compared with female offspring as the reference group. Thus, there seems to be no meaningful alteration in secondary sex ratio based on paternal age. It remains likely that an altered secondary sex ratio is due to a combination of genetics and environmental exposures, which are more likely to explain the declining ratio than advanced paternal age.\(^48\)

The use of the Vital Statistics System for perinatal research has several limitations. The natality database uses birth certificate data that are completed by parents and healthcare workers and these are reviewed for errors but remain susceptible to inaccuracies. This database is also limited to live births, which prevents the inclusion of stillbirths in the analysis. However, as fetal mortality is known to be associated with older mothers could remain. Using regression analysis and stratification, some estimated effects. Finally, despite attempts to adjust for missing paternal data, the potential for overrepresentation of fathers from certain sociodemographic backgrounds remains.\(^3\) Multiple births to the same father are also not accounted for in this study as all data are collected at the maternal level, allowing for the potential bias of some at risk fathers disproportionately contributing to estimated effects. Finally, despite attempts to adjust and account for potential maternal confounding using regression analysis and stratification, some residual confounding effects from older fathers being associated with older mothers could remain.

Conclusions and policy implications

This study evaluated potential fetal-maternal risks associated with advanced paternal age. As more than 12% of births to fathers aged 45 years or older with adverse outcomes might have been prevented were the father younger, the importance of these data are most relevant to parents planning their reproductive future. Preconception counseling guidelines might need to change to incorporate the possibility that delaying parenthood for fathers might not be as consequential as previously understood. The cumulative risk over hundreds of thousands of births to older fathers is also likely to be important in terms of both economic burden and overall public health. While it is important to note that the absolute risk of advancing paternal age on adverse perinatal conditions remains modest, our findings emphasize the need to further investigate the public health implications of increasing paternal age within the US and other countries.

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Ethical approval: Not required.

Data sharing: No additional data available.

Transparency: The lead author (ME) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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dex267/A090627/Age-of-fathers-in-the-USA-is-rising-an.


Supplementary information: additional tables and figure.