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

Yash S Khandwala,[1] Valerie L Baker,[2] Gary M Shaw,[3] David K Stevenson,[3] Ying Lu,[4] Michael L Eisenberg[1,2]

[1]Department of Urology, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118, USA
[2]Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, USA
[3]Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA
[4]Department of Biomedical Data Science, Stanford University School of Medicine, Stanford, CA, USA

Correspondence to:
M L Eisenberg
eisenberg@stanford.edu
(or @drmeisenberg on Twitter)

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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

40 529 905 documented live births between 2007 and 2016.

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.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Mean paternal age in the United States has been increasing for the past 40 years

Though extensive research has been done on the risks of infertility, gestational diabetes, pre-eclampsia, and cesarean delivery for older mothers, little is known about the influence of older fathers on birth outcomes

Recent studies have suggested that epigenetic changes in the sperm of older men might negatively affect placental and embryonic growth

WHAT THIS STUDY ADDS

Men aged 45 years or older had increased odds of fathering infants born premature, of low birth weight, and with a low Apgar score compared with their younger counterparts; the offspring of fathers older than 55 were also more likely to require assisted ventilation and admission to a neonatal intensive care unit

The odds of gestational diabetes was also higher for pregnancies involving fathers older than 45 years

13.2% of premature births and 14.5% of low birth weight infants born to older fathers were estimated to be prevented if all men elected to have children before age 45 years

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.[24]

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 40 529 905 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

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

	Paternal age (years)					
Characteristics	**<25**	**25-34**	**35-44**	**45-54**	**≥55**	**Missing paternal age**
Birth certificates	6 319 860 (15.6)	18 289 776 (45.1)	8 476 310 (20.9)	1 091 848 (2.7)	111 130 (0.3)	6 240 981
Paternal characteristics						
Race:						
White	2 675 449 (42.3)	10 514 234 (57.5)	4 813 626 (56.8)	547 388 (50.1)	51 299 (46.2)	548 536 (8.8)
Black	1 173 282 (18.6)	2 004 854 (11.0)	957 685 (11.3)	197 292 (18.1)	25 535 (23.0)	179 190 (2.9)
Native American	84 260 (1.3)	129 771 (0.7)	44 769 (0.5)	6923 (0.6)	847 (0.8)	13 005 (0.2)
Asian	86 488 (1.4)	961 160 (5.3)	747 699 (8.8)	83 329 (7.6)	8062 (7.3)	74 281 (1.2)
Hispanic	2 046 130 (32.4)	4 178 787 (22.9)	1 667 539 (19.7)	215 563 (19.7)	20 141 (18.1)	244 879 (3.9)
Other or unknown	254 251 (4.0)	500 970 (2.7)	244 992 (2.9)	41 353 (3.8)	5246 (4.7)	5 181 090 (83.0)
Education:						
No high school	1 163 624 (18.4)	1 792 661 (9.8)	720 306 (8.5)	115 949 (10.6)	13 986 (12.6)	22 930 (0.4)
High school	2 897 740 (45.9)	7 152 708 (39.1)	2 693 506 (31.8)	370 827 (34.0)	36 582 (32.9)	48 896 (0.8)
College	105 916 (1.7)	3 898 117 (21.3)	2 555 614 (30.2)	281 475 (25.8)	28 387 (25.5)	5657 (0.1)
Unknown	2 152 580 (34.1)	5 446 290 (29.8)	2 506 884 (29.6)	323 597 (29.6)	32 175 (29.0)	6 163 498 (98.8)
Maternal characteristics						
Age (years):						
<20	5 475 967 (86.7)	3 621 663 (19.8)	324 652 (3.8)	42 161 (3.9)	5478 (4.9)	3 211 653 (51.5)
20-29	808 886 (12.8)	13 646 776 (74.6)	4 407 694 (52.0)	382 294 (35.0)	41 164 (37.0)	2 447 035 (39.2)
30-39	34 765 (0.5)	1 017 567 (5.6)	3 720 600 (43.9)	629 762 (57.7)	58 389 (52.5)	572 413 (9.2)
≥40	242 (0.0)	3770 (0.0)	23 364 (0.3)	37 631 (3.5)	6099 (5.5)	9880 (0.2)
Race:						
White	2 947 988 (46.7)	10 918 297 (59.7)	4 915 885 (58.0)	541 681 (49.6)	45 072 (40.6)	2 407 096 (38.6)
Black	1 038 967 (16.4)	1 753 821 (9.6)	846 975 (10.0)	176 350 (16.2)	23 795 (21.4)	2 074 983 (33.2)
Native American	89 035 (1.4)	135 352 (0.7)	45 390 (0.5)	7022 (0.6)	816 (0.7)	99 588 (1.6)
Asian	131 870 (2.1)	1 178 655 (6.4)	918 320 (10.8)	130 083 (11.9)	18 104 (16.3)	180 402 (2.9)
Hispanic	2 041 846 (32.3)	4 185 812 (22.9)	1 704 974 (20.1)	230 456 (21.1)	22 685 (20.4)	1 417 190 (22.7)
Other or unknown	70 154 (1.1)	117 839 (0.6)	44 766 (0.5)	6256 (0.6)	658 (0.6)	61 722 (1.0)
Education:						
Less than high school	1 615 314 (25.6)	2 142 333 (11.7)	888 685 (10.5)	157 039 (14.4)	19 876 (17.9)	1 571 612 (25.2)
High school	3 974 943 (62.9)	8 863 877 (48.5)	3 222 251 (38.0)	455 578 (41.7)	48 311 (43.5)	2 895 458 (46.4)
College	226 784 (3.6)	5 843 718 (32.0)	3 666 236 (43.3)	384 519 (35.2)	33 158 (29.8)	216 967 (3.5)
Unknown	502 819 (8.0)	1 439 848 (7.9)	699 138 (8.3)	94 712 (8.7)	9785 (8.8)	1 556 944 (24.9)
Median (interquartile range) No of prenatal visits*	11 (9-13)	12 (10-13)	12 (10-14)	12 (9-14)	11 (9-13)	10 (8-13)
Married	2 108 222 (33.4)	13 229 565 (72.3)	6 958 644 (82.2)	835 087 (76.5)	80 465 (72.4)	936 607 (15.0)
Gestational diabetes	185 717 (2.9)	967 204 (5.3)	661 093 (7.8)	104 321 (9.6)	10 746 (9.7)	283 818 (4.5)
Pre-eclampsia	297 358 (4.7)	832 200 (4.6)	385 532 (4.6)	54 894 (5.0)	5769 (5.2)	307 963 (4.9)
Eclampsia	16 938 (0.3)	40 641 (0.2)	20 029 (0.2)	3041 (0.3)	330 (0.3)	21 107 (0.3)
Infant characteristics						
Mean (99% CI) birth weight (g)*	3220 (3219.4 to 3220.6)	3306.6 (3306.3 to 3306.9)	3304.6 (3304.1 to 3305.2)	3253.2 (3251.6 to 3254.8)	3202.4 (3197.4 to 3207.4)	3148.4 (3147.7 to 3149.0)
Mean (99% CI) gestational age (weeks)*	38.69 (38.68 to 38.69)	38.72 (38.72 to 38.72)	38.54 (38.54 to 38.54)	38.36 (38.35 to 38.37)	38.26 (38.24 to 38.28)	38.35 (38.35 to 38.36)
Premature birth (<37 weeks)	745 615 (11.8)	1 902 785 (10.4)	993 011 (11.7)	154 819 (14.2)	17 867 (16.1)	959 100 (15.4)
Low birth weight (<2500 g)	518 957 (8.2)	1 273 508 (7.0)	663 742 (7.8)	107 612 (9.9)	13 031 (11.7)	704 080 (11.3)
Low 5 minute Apgar score (<8)	258 283 (4.1)	617 300 (3.4)	281 172 (3.3)	42 269 (3.9)	4928 (4.4)	295 878 (4.7)
Assisted ventilation	200 197 (3.2)	547 699 (3.0)	259 905 (3.7)	37 986 (3.5)	4178 (3.8)	193 697 (3.1)
Admission to NICU	385 777 (6.1)	1 095 543 (6.0)	563 784 (6.7)	89 329 (8.2)	10 648 (9.6)	424 343 (6.8)
Postpartum antibiotics	116 124 (1.8)	302 290 (1.7)	134 836 (1.6)	19 865 (1.8)	2,235 (2.0)	114 295 (1.8)
Seizures	1715 (0.0)	4409 (0.0)	2000 (0.0)	300 (0.0)	33 (0.0)	1986 (0.0)
Adverse event	524 725 (8.3)	1 449 012 (7.9)	720 770 (8.5)	110 645 (10.1)	12 833 (11.6)	543 107 (8.7)

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.

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

	Paternal age (years)				
Birth outcomes	**<25**	**25-34**	**35-44**	**45-54**	**≥55**
Gestational age coefficient (weeks):					
Unadjusted	−0.03 (−0.04 to −0.03)	Reference	−0.18 (−0.18 to −0.18)	−0.36 (−0.37 to −0.35)	−0.46 (−0.48 to −0.44)
Adjusted	−0.01 (−0.02 to −0.01)	Reference	−0.06 (−0.07 to −0.06)	−0.12 (−0.13 to −0.11)	−0.17 (−0.20 to −0.14)
Birth weight coefficient (g):					
Unadjusted	−86.6 (−87.3 to −85.9)	Reference	−1.97 (−2.59 to −1.34)	−53.4 (−54.9 to −51.9)	−104.2 (−108.7 to −99.7)
Adjusted	−22.9 (−24.1 to −21.7)	Reference	0.95 (−0.02 to 1.91)	−20.2 (−22.5 to −18.0)	−49.2 (−55.9 to −42.5)
Apgar coefficient (5 min):					
Unadjusted	−0.03 (−0.04 to −0.03)	Reference	0.01 (0.00 to 0.01)	−0.02 (−0.03 to −0.02)	−0.05 (−0.06 to −0.05)
Adjusted	−0.02 (−0.02 to −0.02)	Reference	0.01 (0.01 to 0.01)	−0.01 (−0.01 to −0.01)	−0.02 (−0.03 to −0.01)
Premature birth (<37 weeks):					
Unadjusted	1.15 (1.15 to 1.16)	Reference	1.14 (1.14 to 1.15)	1.42 (1.41 to 1.43)	1.65 (1.62 to 1.69)
Adjusted	1.03 (1.02 to 1.04)	Reference	1.06 (1.05 to 1.06)	1.14 (1.13 to 1.15)	1.25 (1.22 to 1.29)
Low birth weight (<2500 g):					
Unadjusted	1.20 (1.19 to 1.20)	Reference	1.14 (1.13 to 1.14)	1.46 (1.45 to 1.47)	1.78 (1.73 to 1.82)
Adjusted	1.05 (1.04 to 1.06)	Reference	1.04 (1.04 to 1.05)	1.14 (1.12 to 1.15)	1.27 (1.22 to 1.31)
Low 5 minute Apgar score (<8):					
Unadjusted	1.23 (1.23 to 1.24)	Reference	0.98 (0.97 to 0.98)	1.15 (1.14 to 1.17)	1.34 (1.29 to 1.39)
Adjusted	1.11 (1.10 to 1.12)	Reference	0.97 (0.96 to 0.98)	1.04 (1.02 to 1.06)	1.14 (1.08 to 1.20)
Assisted ventilation:					
Unadjusted	1.06 (1.05 to 1.07)	Reference	1.02 (1.02 to 1.03)	1.17 (1.15 to 1.18)	1.27 (1.21 to 1.32)
Adjusted	1.04 (1.02 to 1.05)	Reference	1.00 (0.99 to 1.01)	1.06 (1.04 to 1.16)	1.10 (1.04 to 1.16)
Admission to NICU:					
Unadjusted	1.03 (1.03 to 1.04)	Reference	1.12 (1.11 to 1.12)	1.39 (1.38 to 1.40)	1.64 (1.59 to 1.68)
Adjusted	1.01 (1.00 to 1.02)	Reference	1.03 (1.03 to 1.04)	1.14 (1.13 to 1.16)	1.28 (1.24 to 1.33)
Postpartum antibiotics:					
Unadjusted	1.13 (1.12 to 1.14)	Reference	0.96 (0.95 to 0.97)	1.09 (1.07 to 1.11)	1.20 (1.13 to 1.26)
Adjusted	1.04 (1.03 to 1.06)	Reference	0.96 (0.95 to 0.97)	1.03 (1.00 to 1.05)	1.06 (0.99 to 1.14)
Seizures:					
Unadjusted	1.14 (1.06 to 1.22)	Reference	0.98 (0.91 to 1.05)	1.13 (0.97 to 1.32)	1.21 (0.77 to 1.89)
Adjusted	1.06 (0.93 to 1.20)	Reference	1.00 (0.91 to 1.11)	1.18 (0.97 to 1.44)	1.30 (0.77 to 2.20)
Adverse event*:					
Unadjusted	1.05 (1.05 to 1.06)	Reference	1.08 (1.07 to 1.08)	1.31 (1.30 to 1.32)	1.52 (1.48 to 1.55)
Adjusted	1.03 (1.02 to 1.03)	Reference	1.02 (1.01 to 1.02)	1.12 (1.11 to 1.13)	1.24 (1.20 to 1.28)
Gestational diabetes:					
Unadjusted	0.83 (0.82 to 0.83)	Reference	1.15 (1.15 to 1.16)	1.28 (1.27 to 1.29)	1.34 (1.30 to 1.38)
Adjusted	0.82 (0.81 to 0.83)	Reference	1.16 (1.15 to 1.16)	1.28 (1.27 to 1.30)	1.34 (1.29 to 1.38)
Pre-eclampsia:					
Unadjusted	1.04 (1.03 to 1.04)	Reference	1.00 (0.99 to 1.00)	1.11 (1.10 to 1.12)	1.15 (1.11 to 1.19)
Adjusted	1.06 (1.05 to 1.07)	Reference	0.97 (0.96 to 0.97)	0.99 (0.98 to 1.01)	1.00 (0.96 to 1.05)
Eclampsia:					
Unadjusted	1.21 (1.18 to 1.24)	Reference	1.06 (1.04 to 1.09)	1.25 (1.20 to 1.32)	1.34 (1.16 to 1.54)
Adjusted	1.11 (1.06 to 1.16)	Reference	0.99 (0.96 to 1.03)	1.02 (0.95 to 1.10)	1.03 (0.84 to 1.25)

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

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

	Paternal age (years)				
Variables	<25	25-34	35-44	45-54	≥55
No (%) women	4 134 050 (48.7)	10 351 338 (48.8)	4 612 303 (48.8)	603 896 (48.9)	60 795 (48.8)
No (%) men	4 361 018 (51.3)	10 870 121 (51.2)	4 835 218 (51.2)	632 267 (51.1)	64 848 (51.2)
Odds ratio (99% CI)	1.01 (1.00 to 1.01)	Reference	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.00)	1.00 (0.99 to 1.02)

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 stratums for maternal age (fig 1 and supplemental fig 1). Similar findings were noted when the analysis was limited to first births for mothers (see 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.

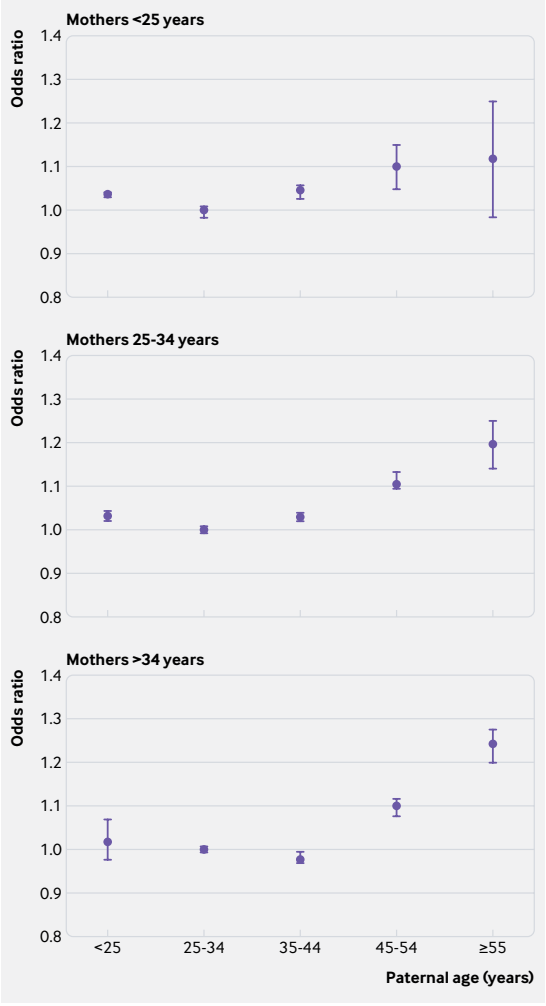

Fig 1 | Scatter plots of odds of an adverse birth event by paternal age stratified by maternal age group. Error bars indicate 99% confidence intervals based on distribution of births within each paternal age group

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 inceased 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 numbers (percentages) unless stated otherwise

Perinatal outcomes	Total No of cases	Paternal age (years)		P value	% of cases prevented if paternal age was <45 (95% CI)
		<45	≥45		
Premature birth (<37 weeks)	4 608 250	4 409 654 (11.3)	198 597 (14.6)	<0.001	13.2 (12.5 to 13.9)
Low birth weight (<2500 g)	3 141 068	3 003 266 (7.7)	137 802 (10.1)	<0.001	14.5 (13.6 to 15.4)
Low 5 minute Apgar score (<8)	1 629 302	1 568 507 (4.0)	60 795 (4.5)	<0.001	5.9 (4.5 to 7.2)
Gestational diabetes	2 225 092	2 095 396 (5.3)	129 696 (9.5)	<0.001	18.2 (17.5 to 18.9)
Pre-eclampsia	1 876 535	1 807 634 (4.6)	68 901 (5.1)	<0.001	3.9 (2.8 to 5.0)
Eclampsia	97 069	93 219 (0.2)	3850 (0.3)	<0.001	5.4 (0.1 to 11.0)
Assisted ventilation	1 483 395	1 426 653 (3.6)	56 742 (4.2)	<0.001	8.6 (7.2 to 9.9)
Admission to NICU	3 035 690	2 901 941 (7.4)	133 749 (9.8)	<0.001	15.1 (14.2 to 15.9)
Postpartum antibiotics	816 272	786 280 (2.0)	29 992 (2.2)	<0.001	6.2 (4.4 to 8.0)
Seizures	11 794	11 348 (0.0)	446 (0.0)	0.04	19.9 (2.9 to 36.7)
Adverse event	3 351 823	3 209 968 (8.2)	141 855 (10.4)	<0.001	12.2 (11.5 to 13.0)

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.[9 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 ages 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, congenital anomaly, genetic disorder, or admission to a neonatal intensive care unit.[39]

Recent studies have begun to uncover a potential epigenetic 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 epigenetic 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 novo 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 advanced paternal age, the inclusion of these data would likely reinforce the findings of this study.[49] Though inverse probability weighting was used to adjust for missing paternal data, the potential for overrepresentation of fathers from certain sociodemographic backgrounds remains.[2] 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 inconsequential 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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Supplementary information: additional tables and figure