Paternal Age and risk of Congenital Anomalies and birth outcomes: A Population-based Cohort Study

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Research Article

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Abstract

Objective: To explore the impact of paternal age on the risk of congenital anomalies and birth outcomes in U.S. infants born between 2016 and 2021.

Methods: This retrospective cohort study was based on live births in the National Vital Statistics System database between 2016 and 2021. All newborns were divided into 4 groups based on paternal age (<25, 25-34, 35-44, and >44 years old groups) and using 25-34 years groups as reference**.** The primary outcomes were congenital anomalies including structural anomalies, and chromosome anomalies, while the secondary outcomes included preterm birth, low birth weight, severe neonatal perinatal asphyxia, admission to neonatal intensive care units, etc. The association between paternal age and outcomes was detected by multivariable logistic analysis.

Results: After the exclusion process, a total of 17,764,695 live births were included in the final analyses. After adjustment for confounding factors, compared with the paternal age of 25-34 years group, advanced paternal age of more than 44 years was associated with increased odds of congenital anomalies (aOR=1.17, 95%CI 1.12-1.21), mainly for the chromosomal anomalies (aOR=1.59, 95%CI 1.40-1.78) but not the structure anomalies (aOR=1.03, 95%CI 0.97-1.09). Advanced paternal age also increased the risk of preterm delivery, low birth weight, and admission to NICU in their infants.

Conclusion: Advanced paternal age increases the risk of congenital anomalies in their offspring, especially chromosomal anomalies, which implies more intensive prenatal or pre-conceptional investigation, including genetic tests, should be taken in the high-risk paternal populations.

What Is Known

It has been documented that the mean paternal age worldwide has been increasing for the past half century, and research has been conducted on the risks associated with birth outcomes such as premature, low birth weight, etc., for older fathers. Despite this, there is limited data on paternal age and congenital abnormalities, and some researchers' conclusions are contradictory.

What is New

Infants of fathers aged 44 years and above were more likely to have congenital anomalies, especially chromosomal anomalies. They were also more likely to be born preterm with lower birth weight and a high chance of being admitted to the NICU. It’d be better for couples to take considerate prenatal or pre-conceptional investigation with paternal age >44 years.

Introduction

With socioeconomic development, life expectancy is gradually improving, and couples tend to have children later in their life [1, 2]. The negative effects of advanced maternal age on the next generation

have been well-known [3–5], however, studies in exploring the effects of paternal age are scarce. There 15% of infants born in England and Wales in 2016 were born to fathers over 40 years old [6], and the average paternal age in 2020 was 33.7 years old across the UK [7]. According to a cohort study conducted in the United States, the average paternal age increased from 27.4 years in 1972 to 30.9 years in 2015, and the percentage of paternal ages more than 40 and 50 years was 8.9% and 0.9% respectively [8]. Considering the rising prevalence of advanced paternal age, it is essential to assess how it impacts future generation [9].

It has been found that higher paternal age is associated with a number of diseases in their children, including schizophrenia [10], autism [11], intellectual disabilities [12], and achondroplasia [13], premature birth [14, 15], low birth weight [16], birth defects [17, 18], congenital heart disease [19], childhood malignancies [20–22], abortion [23] and decreased success rates of artificially assisted reproduction [6]. Since congenital anomalies are the second most common etiology of neonatal death only after preterm birth [24] and also contribute significantly to early childhood deaths and long-term disabilities in children [25], determining the relationship between paternal age and congenital anomalies and birth conditions could be beneficial in guiding family fertility and prenatal consultation.

Materials And Methods

Study population

This retrospective cohort analysis was based on the National Vital Statistics System (NVSS), a federal data-sharing program offered by the Centers for Disease Control and Prevention and the National Center for Health Statistics, which contains birth and death records that are electronically submitted by the 50 states and the District of Columbia [26]. The National Center for Health Statistics compiles live birth data from birth certificates and allows the distribution of these statistics for medical research purposes, so they are not subject to ethical review or informed consent requirements.

In particular, for this study, we collected birth information and health characteristics for all fathers and infants in the database. We extracted the available demographic characteristics, such as parents' age, race, education level, gestational diseases, method of pregnancy, and so on across all live births reported in the United States from 2016 to 2021. The classification of paternal age was done in 10-year increments: 25 years, 25-34 years, 35-44 years, and >44 years. Records that did not provide paternal age or other information about fertility treatment were excluded (Figure 1).

Outcomes

As the main purpose of this study was to examine the relationship between advanced paternal age and neonatal congenital anomalies and birth conditions. The primary outcomes were congenital anomalies including structural anomalies (SAs), and chromosome anomalies (ChAs), while the secondary outcomes were preterm birth, low birth weight, severe neonatal asphyxia, and admission to the neonatal intensive care unit (NICU). Congenital anomalies (CAs) included neonatal malformations diagnosed before or after

delivery. SAs included anencephaly, myelomeningocele/spina bifida, cyanotic congenital heart disease, congenital diaphragmatic hernia, omphalocele, gastroschisis, limb reduction defect, cleft lip with or without cleft palate, cleft palate alone, hypospadias, while ChAs included Down syndrome and suspected chromosomal disorders. Preterm birth was subdivided into gestational age <37 weeks and gestational age <28 weeks. Low birth weight was subdivided into birth weight <2500 g and birth weight <1500 g. Severe neonatal asphyxia was defined as a 5-minute Apgar score ≤3. Admission to the NICU was admission to the NICU at any time during the hospital stay after delivery. All data were collected directly from the database, all outcome variables were classified as dichotomous variables, and specific definitions of relevant diseases refer to the Medical and Health Information section of the US Standard Certificate of Live Birth.

Covariables

The following variables were identified as potential confounding factors: maternal age, parents' race and ethnicity, education level, maternal pre-pregnancy body mass index (BMI), gestational hypertension, eclampsia, gestational diabetes, the mode of conception, and newborn sex. The maternal age was divided into four categories: 25, 25-34, 35-44, and >44. Parents' race and ethnicity were self-reported in the database, and we classified them as White, Black, Asian, and Others who did not specify their race or ethnicity or who did so but then have at least two races. Parents' educational levels were recorded as lower than high school diploma, high school diploma, or higher than high school diploma. Maternal pre-pregnancy BMI was classified into three categories: 18.5, 18.5-24.9, >24.9 Kg/m^2. The methods of pregnancy were classified as natural conception or acceptance of infertility treatment (including the use of fertility-enhancing drugs and the use of artificial assisted reproductive technology). Gestational diabetes, gestational hypertension, and hypertension eclampsia were classified as yes or no. The gender of the infants was classified as male or female. These parents' variables were extracted from the Facilities worksheet of the United States Live Birth Standards Certificate.

Statistical Analyses

The statistical analysis was conducted with Stata version 17.0 (Stata Corp LLC). All P values were bilateral, and $P < 0.05$ was considered statistically significant. We reported the mean and standard deviation of continuous variables and the frequency and percentage of categorical variables. Differences were tested using the $\chi 2$ test for categorical variables and the t-test or analysis of variance was used for numerical variables.

As a summary cohort, we analyzed the mean paternal age and standard deviation for all live births from 2016 to 2021. To determine the association between paternal age and congenital anomalies and birth outcomes, we developed a logistic regression model using the paternal age of 25 to 34 years as a reference group to estimate the adjusted odds ratios for each outcome. The variables were adjusted for sociodemographic characteristics, including maternal age, parents' race and ethnicity, parents' education level, gestational hypertension, gestational diabetes, hypertension eclampsia, the mode of conception,

and infant gender. In light of the lack of information available in the 2020 database regarding ChAs, the correlation analysis of ChAs was performed by means of a user-written mlogit language package for disordered logistic regression analysis. Furtherly, we conducted sensitivity analyses and subgroup analyses based on baseline characteristics for congenital, structural, and chromosomal anomalies, which were adjusted for potential risk factors to determine if covariates were associated with primary outcomes and to verify whether the results were robust.

Results

Between 2016 and 2021, 22,669,793 live births were registered in NVSS. After the exclusion process, 17,764,695 live births were included in the final analyses (Figure 1). Table 1 demonstrated the paternal, maternal, and infant characteristics. Of all live births, 3.9% were with paternal age more than 44 years old.

After adjusting for confounding factors, the risk of congenital anomalies increased significantly in the paternal ages of more than 44 years group compared with the control 25 to 34 years group (aOR=1.17, 95%CI 1.12-1.21) (Table 2) mainly for the ChAs (aOR=1.59, 95%CI 1.40-1.78) but not for SAs (aOR= 1.03, 95%CI 0.97-1.09). For secondary outcomes, high paternal age of more than 44 years was associated with a higher risk of preterm delivery with gestational age less than 37 w and 28 w (aOR=1.09, 95%CI 1.08-1.10; aOR=1.06, 95%CI 1.03-1.09), lower birth weight <2500 g and <1500 g (aOR=1.11, 95%CI 1.10-1.12; aOR=1.06, 95%CI 1.04-1.08) and a higher chance of admission to NICU (aOR=1.13, 95%CI 1.12-1.14).

In subgroup analyses, the population was stratified by maternal age, parents' race and ethnicity, parents' education level, gestational hypertension, gestational diabetes, hypertension eclampsia, the mode of conception, and newborn sex. Infants born in the higher paternal age group have a greater risk of primary outcomes, especially when combined with high maternal age of more than 35 years old, high maternal pregnancy BMI>24.9, and maternal hypertension eclampsia, etc. (Table 3).

Considering that gestational diabetes, gestational hypertension, and hypertension eclampsia were binary variables, sensitivity analysis was mainly conducted based on maternal age, parents' race and ethnicity, parents' education level, and maternal prenatal BMI. Factoring out the above variables, high paternal age still showed a higher risk of CAs, especially ChAs, consistent with the main results (Table 4).

Discussion

Based on the large-sample live birth registration of NVSS, we found that advanced paternal age significantly increased the risk of CAs among newborns, especially ChAs. In addition, advanced paternal age increased the risk of preterm delivery, low birth weight infants, and admission to NICU as well.

The result of the current study on the negative impact of advanced paternal age on congenital anomalies of offspring was consistent with previous publications. Sloter [27] proposed in 2004 that congenital anomaly may increase with increasing paternal age, and our study confirmed this hypothesis. Khandwala [14] noted in a large cohort study that the odds ratio is less than 1.5, suggesting that risk is still low. In

this study, the odds ratio of ChAs after adjusted risk factors was 1.59. Therefore, there is a certain degree of confidence about the impact of advanced paternal age more than 44 years old on ChAs in offspring. The SAs were not significantly increased in the advanced paternal age. The potential reason is that SAs could be more easily detected by prenatal ultrasound or MRI, resulting in medical abortion, compared with ChAs which only could be detected by genetic tests not being as commonly used as prenatal ultrasound.

According to previous studies, the overall prevalence of birth defects in live births ranges between 3–5% [28], and in this study, the overall prevalence of CAs from 2017 to 2021 was 0.33%. It may be that the definition of birth defect has not been agreed upon. Yang [24] published a population-based retrospective cohort study based on 5 million infants, which found that advanced paternal age was associated with an increased risk of birth defects. Hurley [22] also found that the relative risk of congenital anomalies increased with increased paternal age.

The etiology of advanced paternal age increasing the risk of congenital anomalies in infants lies in methylation defects in sperm DNA [29]. Fang's meta-analysis results [18] demonstrated that men were exposed to more harmful physical, chemical, and biological factors in the environment with age increasing. Antioxidant capacity decreased with aging which can lead to DNA damage. Additionally, sperm continuously divide during the reproductive cycle, thus increasing cell division [2] and the premeiotic process involves multiple asymmetric spermatogonia divisions which enable sperm to acquire new single nucleotide variants or mutations. A study by Stabile [30] demonstrated that increasing paternal age affected sperm motility, velocity, and coordination in mice, and reduced in vitro embryonic development and fetal body weight in mice. Furthermore, genetic mutations occur when mistakes take place in post-meiotic chromatin remodeling and DNA repair [31], and sperm from elder men are also more likely to have chromosome aneuploidy, which may be the cause of chromosome anomalies in the next generation [32].

The result of this study also demonstrated that advanced paternal age increased the risk of preterm and low birth weight deliveries. The effect of high paternal age on preterm birth has generally been affirmed in previous research [14, 33]. In this study, for outcomes of gestational age less than 37 weeks and less than 28 weeks, the aORs were 1.09 and 1.06. In spite of the minimal impacts, the results remained steady. Prematurity is the leading cause of infant death in the United States, which also could be related to bronchopulmonary dysplasia and cerebral palsy, etc. causing social and economic burdens to the society [2, 34]. Furthermore, a retrospective study by Mao [33] showed that advanced paternal age could increase the risk of low birth weight babies for gestational age not only in preterm infants but also in term infants.

We also detected the impact of advanced paternal age on perinatal asphyxia and NICU admission. Studies on the effect of paternal age on Apgar score were limited [35]. And in this research, no impact of advanced paternal age on the low Apgar score in their infants was appreciated. However, this study showed that advanced paternal age significantly increased the risk of offspring requiring admission to NICU, which is consistent with previous study [14].

Our study had obvious limitations. Firstly, the association between advanced paternal age and negative infant outcomes was detected, but the etiology and cause-effect relationship need to be further investigated. Furthermore, a more detailed classification of structural and chromosomal anomalies has not been made and the effect of paternal age on a specific congenital anomaly has not been conducted. Finally, the database was not designed for detecting the impact of advanced paternal age, as such, missing data, especially lacking data on congenital anomalies in the whole year of 2020, potentially caused selection bias. Otherwise, due to the increasing trend of paternal age in developed countries [7], our study based on a large population of more than 17 million on advanced paternal age did provide valuable data for guiding pre-conceptional and prenatal consultation.

In conclusion, advanced paternal age increases the risk of congenital anomalies in their offspring, especially the prevalence of chromosomal anomalies, which implies more intensive prenatal or pre-conceptional investigation, including genetic tests, should be taken in the high-risk paternal populations.

Abbreviations

aOR Adjusted odds ratio

BMI Body mass index

CAs Congenital anomalies

ChAs Chromosome anomalies

CI Confidence interval

NICU Neonatal intensive care unit

NVSS National Vital Statistics System

PA Paternal age

SAs Structural anomalies

Declarations

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Competing interests

None of the authors have relevant financial or non-financial interests to disclose.

Author contributions

All authors contributed to the final draft during the writing and reviewing of the paper. Specific contributions are as follows. It was JGZ who developed the conceptual framework and supervised the writing process. The first draft of the manuscript was written by XHB and all authors commented on previous versions of the manuscript. XHB and JGZ provided statistical and methodological advice on the use of routine vital event data and potential sources of bias. The overall management of the population cohort is performed by XHB and WJY, as well as ensuring that the reports are accurate. JGZ conceived the original concepts for the paper.

Ethics approval

Since the data used in the study was publicly available and the study involved no human subjects, the Children's Hospital of Fudan University Institutional Review Board waived the informed consent requirement.

Consent to publish

The Author confirms:

That the work described has not been published before;

that it is not under consideration for publication elsewhere;

that its publication has been approved by all co-authors;

that its publication has been approved (tacitly or explicitly) by the responsible authorities at the institution where the work is carried out.

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Tables

Table 1. Population Characteristics of included cases

Characteristic	PA 25y	PA 25-34y	PA 35-44y	PA 44y
Total	2429459 (13.7)	9633983 (54.2)	5016616 (28.2)	684637 (3.9)
Birth year of neonate				
2016	367577 (15.1)	1559836 (16.2)	852727 (17.0)	107139 (15.7)
2017	367301 (15.1)	1518398 (15.8)	816060 (16.2)	108846 (15.9)
2018	399791 (16.5)	1590362 (16.5)	840250 (16.7)	115320 (16.8)
2019	409917 (16.9)	1622670 (16.9	842775 (16.8)	117654 (17.2)
2020	431434 (17.8)	1651074 (17.1)	833857 (16.7)	118117 (17.2)
2021	453439 (18.6)	1691643 (17.5)	830947 (16.6)	117561 (17.2)
Paternal age, mean (SD), y	21.9 (1.9)	29.9 (2.8)	38.1 (2.6)	48.9 (4.3)
Maternal age, mean (SD), y	21.8 (3.1)	28.6 (3.9)	33.9 (4.2)	36.0 (5.4)
Father Race and ethnicity				
White	1723906 (71.0)	7392623 (76.7)	3704426 (73.8)	443848 (64.8)
Black	529717 (21.8)	1324964 (13.6)	663543 (13.2)	153683 (22.4)
Asian	31081 (1.3)	580387 (6.0)	507631 (10.1)	67212 (9.8)
Other	144755 (5.9)	336009 (3.5)	141016 (2.9)	19894 (3.0)
Mother Race and ethnicity				
White	569359 (23.4)	2416575 (25.1)	1224589 (24.5)	142287 (20.8)
Black	140838 (5.8)	377242 (3.9)	194847 (3.9)	45693 (6.7)
Asian	10596 (0.5)	201716 (2.1)	187691 (3.8)	29122 (4.2)
Other	1708666 (70.3)	6638450 (68.9)	3409489 (67.8)	467535 (68.3)

Father Educational diploma level				
< High school	522945 (21.5)	888372 (9.2)	433855 (8.7)	84126 (12.3)
High school	1281109 (52.7)	2784433 (28.9)	1033949 (20.6)	169651 (24.8)
> High school	625405 (25.8)	5961178 (61.9)	3548812 (70.7)	430860 (62.9)
Mother Educational diploma level				
High school	462339 (19.0)	716783 (7.5)	367250 (7.3)	83638 (12.2)
High school	1098167 (45.2)	2111741 (21.9)	758206 (15.1)	139331 (20.4)
High school	868953 (35.8)	6805459 (70.6)	3891160 (77.6)	461668 (67.4)
Mather pregnancy BMI				
18.5	125976 (5.2)	271337 (2.8)	116592 (2.3)	19575 (2.9)
18.5-24.9	1034687 (42.6)	4105741 (42.6)	2186722 (43.6)	283971 (41.4)
24.9	1268796 (52.2)	5256905 (54.6)	2713302 (54.1)	381091 (55.7)
Gestational hypertension				
Yes	193112 (7.9)	712115 (7.4)	363668 (7.2)	631117 (92.2)
No	2236347 (92.1)	8921868 (92.6)	4652948 (92.8)	53520 (7.8)
Gestational diabetes				
Yes	93253 (3.8)	632913 (6.6)	468270 (9.3)	76317 (11.1)
No	2336206 (96.2)	9001070 (93.4)	4548346 (90.7)	608320 (88.9)
Hypertension Eclampsia				
Yes	7279 (0.3)	23542 (0.3)	12907 (0.3)	2102 (0.3)
No	2422180 (99.7)	9610441 (99.7)	5003709 (99.7)	682535 (99.7)
Infertility Treatment Used				
Yes	3983 (0.2)	152722 (1.6)	196063 (3.9)	43167 (6.3)

No	2425476 (99.8)	9481261 (98.4)	4820553 (96.1)	641470 (93.7)
Infant Gender				
Male	1245278 (51.3)	4935513 (51.2)	2567042 (51.2)	349354 (51.1)
Female	1184181 (48.7)	4698470 (48.8)	2449574 (48.8)	335283 (48.9)
Low birth weight infant				
No	2226221 (91.6)	8955148 (93.0)	4631572 (92.3)	617765 (90.2)
Yes	203238 (8.4)	678835 (7.0)	385044 (7.7)	66872 (9.8)
Preterm birth				
No	2200542 (90.6)	8781757 (91.2)	4523722 (90.2)	602359 (88.0)
Yes	228917 (9.4)	852226 (8.8)	492894 (9.8)	82278 (12.0)

PA, Paternal age.

Table 2. Paternal age and risk of primary and secondary outcomes using 25 to 34 year age group as reference

Outcomes	25		25-34 as reference	35-44		44	
	N%	aOR	N%	N%	aOR	N%	aOR
Primary outcomes							
CAs	8071 (0.33)	1.02 (1.01-1.03)	29693 (0.31)	17987 (0.36)	1.01 (0.99-1.03)	3128 (0.45)	1.17 (1.12-1.21)
SAs	5945 (0.24)	1.04 (1.00-1.08)	20616 (0.21)	10556 (0.21)	0.99 (0.96-1.02)	1532 (0.22)	1.03 (0.97-1.09)
ChAs	379 (0.016)	1.01 (0.88-1.17)	1894 (0.020)	1994 (0.040)	1.08 (1.00-1.16)	518 (0.076)	1.59 (1.40-1.78)
Secondary outcomes							
GA < 37w	228917 (9.4)	1.05 (1.04-1.06)	852226 (8.8)	492894 (9.8)	1.01 (1.00-1.02)	82278 (12.0)	1.09 (1.08-1.10)
GA < 28w	14865 (0.6)	1.06 (1.04-1.08)	45903 (0.48)	25295 (0.50)	0.99 (0.98-1.00)	4631 (0.68)	1.06 (1.03-1.09)
BW < 2500g	203238 (8.4)	1.05 (1.04-1.06)	678835 (7.0)	385044 (7.7)	1.01 (1.00-1.02)	66872 (9.8)	1.11 (1.10-1.12)
BW < 1500g	14987 (0.61)	1.06 (1.04-1.08)	46780 (4.9)	25945 (0.52)	0.99 (0.98-1.00)	4800 (0.70)	1.06 (1.04-1.08)
Admission to NICU	2023921 (8.4)	1.02 (1.01-1.03)	783689 (8.1)	449277 (9.0)	1.02 (1.01-1.03)	74966 (10.9)	1.13 (1.12-1.14)
5min Apgar score ≤ 3	9575 (0.39)	1.08 (1.05-1.11)	29596 (0.31)	15366 (0.31)	0.98 (0.96-1.00)	2545 (0.71)	1.02 (0.98-1.06)

PA, paternal age; CAs, congenital anomalies; SAs, structure anomalies; ChAs, chromosomal anomalies; GA, gestational age. aOR, adjusted odds ratio, adjusted for sociodemographic characteristics, including maternal age, parents' race and ethnicity, parents' education level, gestational hypertension, gestational diabetes, hypertension eclampsia, mode of conception, and infant gender.

Table 3. Paternal age and risks of CAs, SAs or ChAs subgroup analyses using paternal age of 25 to 34-year group as reference

Subgroups	Paternal age < 25			35-44			> 44		
	CAs	SAs	ChAs	CAs	SAs	ChAs	CAs	SAs	ChAs
Maternal age									
25y	1.03 (0.99-1.07)	1.04 (0.99-1.09)	1.04 (0.87-1.21)	1.07 (0.97-1.17)	1.08 (0.96-1.20)	1.20 (0.76-1.64)	0.99 (0.77-1.24)	0.90 (0.66-1.14)	1.12 (0.36-1.88)
25-34y	1.03 (0.97-1.09)	1.06 (0.98-1.14)	1.01 (0.78-1.24)	0.99 (0.96-1.02)	0.96 (0.93-0.99)	1.04 (0.94-1.14)	1.02 (0.94-1.10)	1.01 (0.92-1.10)	1.20 (0.90-1.50)
35-44y	1.16 (0.91-1.41)	1.11 (0.78-1.44)	1.41 (0.79-2.03)	1.12 (1.07-1.17)	1.07 (1.01-1.13)	1.16 (1.03-1.29)	1.32 (1.24-1.40)	1.10 (1.01-1.19)	1.75 (1.51-1.99)
44y	1.14 (0.90-1.38)	1.11 (0.77-1.45)	1.36 (0.77-1.95)	1.13 (1.07-1.19)	1.80 (0.64-2.96)	1.08 (0.41-1.75)	1.32 (1.22-1.42)	2.09 (1.77-2.41)	1.46 (1.39-1.53)
Father Race and ethnicity									
White	1.02 (0.99-1.05)	1.05 (1.01-1.09)	0.95 (0.81-1.09)	1.00 (0.98-1.02)	0.98 (0.96-1.00)	1.03 (0.95-1.11)	1.14 (1.09-1.19)	1.02 (0.96-1.08)	1.45 (1.27-1.63)
Black	1.01 (0.93-1.09)	1.00 (0.92-1.08)	1.34 (0.96-1.72)	1.05 (0.98-1.12)	1.02 (0.94-1.10)	1.18 (0.94-1.42)	1.20 (1.08-1.32)	1.02 (0.90-1.14)	1.91 (1.46-2.36)
Asian	0.92 (0.71-1.13)	1.02 (0.74-1.66)	1.39 (0.43-2.35)	1.00 (0.91-1.09)	0.98 (0.87-1.09)	1.36 (0.92-1.80)	1.23 (1.04-1.42)	0.98 (0.78-1.18)	2.30 (1.37-3.23)
Other	1.06 (0.93-1.19)	1.02 (0.87-1.17)	1.08 (0.58-1.58)	1.07 (0.95-1.19)	1.01 (0.87-1.15)	1.73 (1.15-2.31)	1.30 (1.04-1.56)	1.10 (0.82-1.38)	1.99 (1.02-2.96)
Mother Race and ethnicity									
White	1.05 (0.99-1.11)	1.09 (1.00-1.18)	1.08 (0.64-1.44)	1.00 (0.95-1.05)	0.97 (0.88-1.06)	1.11 (0.83-1.28)	1.09 (0.99-1.19)	0.95 (0.82-1.08)	1.72 (1.10-2.34)
Black	0.96 (0.81-1.11)	0.90 (0.72-1.08)	0.76 (0.25-1.27)	1.07 (0.95-1.19)	1.06 (0.89-1.23)	0.87 (0.39-1.35)	1.32 (1.10-1.54)	1.35 (1.02-1.68)	1.49 (0.55-2.43)
Asian	1.42 (0.95-1.89)	1.85 (1.07-2.63)	1.01 (0.87-1.15)	1.09 (0.93-1.25)	1.02 (0.82-1.22)	2.87 (1.73-4.73)	1.34 (1.04-1.64)	1.15 (0.80-1.45)	1.81 (0.19-3.43)
Other	1.01 (0.97-1.05)	1.03 (0.99-1.07)	1.02 (0.88-1.16)	1.01 (0.99-1.03)	0.99 (0.96-1.01)	1.06 (0.98-1.14)	1.17 (1.12-1.22)	1.03 (0.96-1.10)	1.56 (1.38-1.74)

Father Educational diploma level									
High school	1.05 (0.98-1.12)	1.09 (1.00-1.18)	0.91 (0.67-1.15)	1.08 (1.01-1.15)	0.99 (0.91-1.07)	1.21 (0.98-1.44)	1.25 (1.13-1.37)	1.06 (0.91-1.21)	1.56 (1.17-1.95)
High school	1.01 (0.97-1.05)	1.02 (0.97-1.07)	0.94 (0.76-1.12)	1.05 (1.01-1.09)	1.02 (0.97-1.07)	1.20 (1.03-1.37)	1.16 (1.07-1.25)	0.98 (0.88-1.08)	1.80 (1.45-2.15)
High school	1.06 (1.00-1.12)	1.05 (0.98-1.12)	1.33 (1.05-1.61)	0.99 (0.96-1.02)	0.98 (0.94-1.12)	1.01 (0.92-1.10)	1.14 (1.07-1.21)	1.04 (0.96-1.12)	1.49 (1.29-1.69)
Mother pre-pregnancy BMI									
18.5	1.07 (0.93-1.21)	1.16 (0.98-1.34)	0.79 (0.40-1.18)	0.92 (0.80-1.04)	1.00 (0.84-1.16)	0.53 (0.29-0.77)	0.89 (0.67-1.11)	0.96 (0.68-1.24)	0.57 (0.21-0.93)
18.5-24.9	0.99 (0.94-1.04)	1.02 (0.97-1.07)	0.82 (0.66-0.98)	0.97 (0.94-1.00)	0.97 (0.93-1.01)	0.99 (0.88-1.10)	1.08 (1.01-1.15)	0.98 (0.89-1.07)	1.32 (1.10-1.54)
24.9	1.03 (0.98-1.08)	1.03 (0.98-1.08)	1.23 (1.02-1.44)	1.04 (1.01-1.07)	1.00 (0.97-1.06)	1.17 (1.06-1.28)	1.24 (1.17-1.31)	1.07 (1.00-1.14)	1.82 (1.58-2.06)
Gestational hypertension									
Yes	1.01 (0.91-1.11)	1.04 (0.92-1.16)	1.43 (0.91-1.94)	1.02 (0.95-1.09)	0.97 (0.89-1.05)	1.34 (1.03-1.65)	1.20 (1.06-1.34)	1.07 (1.01-1.13)	1.85 (1.25-2.45)
No	1.01 (0.98-1.04)	1.03 (0.99-1.07)	0.98 (0.84-1.12)	1.01 (0.99-1.03)	0.99 (0.96-1.02)	1.05 (0.97-1.13)	1.16 (1.11-1.21)	1.02 (0.96-1.08)	1.54 (1.37-1.71)
Gestational diabetes									
Yes	1.04 (0.90-1.18)	1.04 (0.88-1.20)	2.07 (1.22-2.93)	1.05 (0.98-1.12)	1.00 (0.92-1.08)	1.04 (0.81-1.27)	1.17 (1.05-1.29)	1.04 (0.98-1.10)	1.42 (1.01-1.83)
No	1.02 (0.98-1.06)	0.97 (0.95-0.99)	0.97 (0.84-1.10)	1.01 (0.98-1.04)	0.98 (0.95-1.01)	1.08 (1.00-1.16)	1.16 (1.11-1.21)	0.96 (0.81-1.11)	1.59 (1.41-1.77)
Hypertension Eclampsia									
Yes	1.11 (0.61-1.51)	0.98 (0.50-1.46)	1.48 (0.09-2.87)	1.30 (0.88-1.72)	1.10 (0.70-1.50)	2.16 (0.49-3.83)	1.60 (1.36-1.84)	1.62 (1.51-1.71)	1.98 (1.44-2.52)
No	1.02 (0.99-1.05)	1.04 (1.00-1.08)	1.01 (0.88-1.14)	1.01 (0.98-1.04)	0.99 (0.96-1.02)	1.07 (1.00-1.14)	1.16 (1.12-1.20)	1.03 (0.94-1.12)	1.57 (1.40-1.74)
Infertility Treatment Used									

Yes	1.23 (0.76-1.70)	1.32 (0.76-1.88)	1.18 (0.13-2.23)	0.96 (0.86-1.06)	0.96 (0.84-1.08)	0.78 (0.51-1.07)	1.02 (0.85-1.19)	1.07 (0.97-1.17)	1.08 (0.62-1.54)
No	1.02 (0.99-1.05)	1.04 (1.00-1.08)	1.02 (0.89-1.15)	1.01 (0.99-1.03)	0.99 (0.96-1.02)	1.08 (1.00-1.16)	1.18 (1.13-1.23)	1.02 (0.97-1.08)	1.59 (1.42-1.76)
Gender									
Male	1.00 (0.96-1.04)	1.02 (0.98-1.06)	0.99 (0.81-1.17)	1.00 (0.97-1.03)	0.94 (0.89-0.99)	1.06 (0.96-1.16)	1.12 (1.06-1.18)	1.01 (0.92-1.10)	1.43 (1.21-1.65)
Female	1.05 (1.00-1.10)	1.07 (1.00-1.14)	1.04 (0.85-1.23)	1.03 (0.99-1.07)	1.00 (0.85-1.15)	1.09 (0.98-1.20)	1.24 (1.17-1.31)	1.07 (0.97-1.17)	1.73 (1.47-1.99)

CAs, congenital anomalies; SAs, structure anomalies; ChAs, chromosomal anomalies. BMI, body mass index.

Table 4. The result of Sensitivity Analyses in CAs, SAs, and ChAs using paternal age of 25 to 34-year group as reference

	PA < 25			35-44			> 44		
	CAs	SAs	ChAs	CAs	SAs	ChAs	CAs	SAs	ChAs
Exclude the Maternal age of									
25y	1.02 (0.96-1.08)	1.05 (0.98-1.12)	1.02 (0.80-1.24)	1.01 (0.99-1.03)	0.98 (0.95-1.01)	1.07 (1.00-1.14)	1.16 (1.12-1.18)	1.03 (0.97-1.09)	1.56 (1.40-1.72)
25-34y	1.01 (0.98-1.04)	1.03 (0.99-1.07)	1.03 (0.87-1.19)	1.09 (1.05-1.13)	1.07 (1.01-1.13)	1.15 (1.03-1.27)	1.30 (1.23-1.37)	1.09 (1.01-1.17)	1.72 (1.50-1.94)
35-44y	1.02 (0.99-1.05)	1.04 (1.00-1.08)	1.02 (0.87-1.17)	0.99 (0.97-1.01)	0.97 (0.94-1.00)	1.05 (0.95-1.15)	1.02 (0.96-1.08)	1.01 (0.93-1.09)	1.25 (1.00-1.50)
44y	1.02 (0.98-1.06)	1.03 (1.00-1.06)	1.02 (0.88-1.16)	1.00 (0.99-1.01)	0.99 (0.96-1.02)	1.07 (0.99-1.15)	1.17 (1.12-1.22)	1.02 (0.97-1.07)	1.57 (1.40-1.74)
Exclude Father Race and ethnicity of									
White	1.00 (0.94-1.06)	1.00 (0.93-1.07)	1.26 (0.95-1.57)	1.04 (0.99-1.09)	1.00 (0.95-1.05)	1.28 (1.08-1.48)	1.23 (1.14-1.32)	1.03 (0.93-1.13)	2.04 (1.63-2.45)
Black	1.02 (0.98-1.06)	1.04 (1.01-1.07)	0.96 (0.82-1.10)	1.01 (0.98-1.04)	0.98 (0.95-1.01)	1.06 (0.98-1.14)	1.15 (1.10-1.20)	1.02 (0.96-1.08)	1.50 (1.33-1.67)
Asian	1.02 (0.99-1.05)	1.03 (1.00-1.06)	1.01 (0.88-1.14)	1.01 (0.99-1.03)	0.99 (0.96-1.02)	1.07 (0.99-1.15)	1.16 (1.11-1.21)	1.03 (0.97-1.09)	1.54 (1.37-1.71)
Other	1.02 (0.98-1.04)	1.04 (0.99-1.09)	1.01 (0.87-1.15)	1.00 (0.98-1.02)	0.98 (0.96-1.00)	1.06 (0.98-1.14)	1.16 (1.10-1.22)	1.02 (0.97-1.07)	1.55 (1.39-1.71)
Exclude Mother Race and ethnicity of									
White	1.01 (0.97-1.05)	1.03 (0.98-1.08)	1.01 (0.87-1.15)	1.02 (0.99-1.05)	0.99 (0.96-1.02)	1.07 (0.99-1.15)	1.19 (1.14-1.24)	1.04 (0.98-1.10)	1.56 (1.39-1.73)
Black	1.02 (0.99-1.05)	1.04 (1.00-1.08)	1.02 (0.88-1.16)	1.00 (0.98-1.02)	0.98 (0.96-1.00)	1.08 (1.00-1.16)	1.16 (1.11-1.21)	1.01 (0.96-1.06)	1.57 (1.40-1.74)
Asian	1.01 (0.98-1.04)	1.03 (1.00-1.06)	1.02 (0.89-1.15)	1.01 (0.99-1.03)	0.99 (0.96-1.02)	1.06 (0.97-1.15)	1.16 (1.12-1.20)	1.02 (0.97-1.07)	1.56 (1.40-1.72)
Other	1.04 (0.98-1.10)	1.07 (0.99-1.15)	0.98 (0.61-1.35)	1.01 (0.97-1.05)	0.98 (0.92-1.04)	1.21 (0.93-1.49)	1.15 (1.07-1.23)	1.03 (0.92-1.14)	1.71 (1.14-2.18)

Exclude Father Educational diploma level of									
High school	1.02 (0.98-1.04)	1.03 (0.98-1.08)	1.06 (0.91-1.21)	1.00 (0.98-1.02)	0.99 (0.96-1.02)	1.06 (0.98-1.14)	1.15 (1.10-1.20)	1.02 (0.96-1.08)	1.57 (1.39-1.75)
High school	1.03 (0.99-1.07)	1.06 (1.00-1.12)	1.10 (0.91-1.29)	1.00 (0.97-1.03)	0.98 (0.96-1.00)	1.04 (0.95-1.13)	1.16 (1.10-1.22)	1.04 (0.98-1.10)	1.50 (1.31-1.69)
High school	1.02 (0.99-1.05)	1.04 (1.00-1.08)	0.93 (0.78-1.22)	1.06 (1.02-1.10)	1.02 (0.97-1.07)	1.20 (1.06-1.34)	1.20 (1.12-1.28)	1.01 (0.92-1.10)	1.70 (1.43-1.97)
Exclude Mother pre-pregnancy BMI of									
18.5	1.01 (0.98-1.04)	1.03 (1.00-1.06)	1.03 (0.89-1.17)	1.01 (0.99-1.03)	0.99 (0.96-1.02)	1.09 (1.01-1.17)	1.17 (1.13-1.21)	1.03 (0.97-1.09)	1.60 (1.43-1.77)
18.5-24.9	1.04 (0.99-1.08)	1.04 (1.00-1.08)	1.19 (0.99-1.39)	1.04 (1.01-1.07)	1.00 (0.97-1.03)	1.14 (1.04-1.24)	1.22 (1.16-1.28)	1.06 (0.99-1.13)	1.76 (1.52-2.00)
24.9	1.00 (0.96-1.04)	1.04 (0.99-1.09)	0.81 (0.66-0.96)	0.97 (0.94-1.00)	0.97 (0.93-1.01)	0.97 (0.86-1.08)	1.07 (1.00-1.14)	0.98 (0.90-1.06)	1.27 (1.06-1.48)

CAs, congenital anomalies; SAs, structure anomalies; ChAs, chromosomal anomalies; PA, paternal age; BMI, body mass index.

Figures

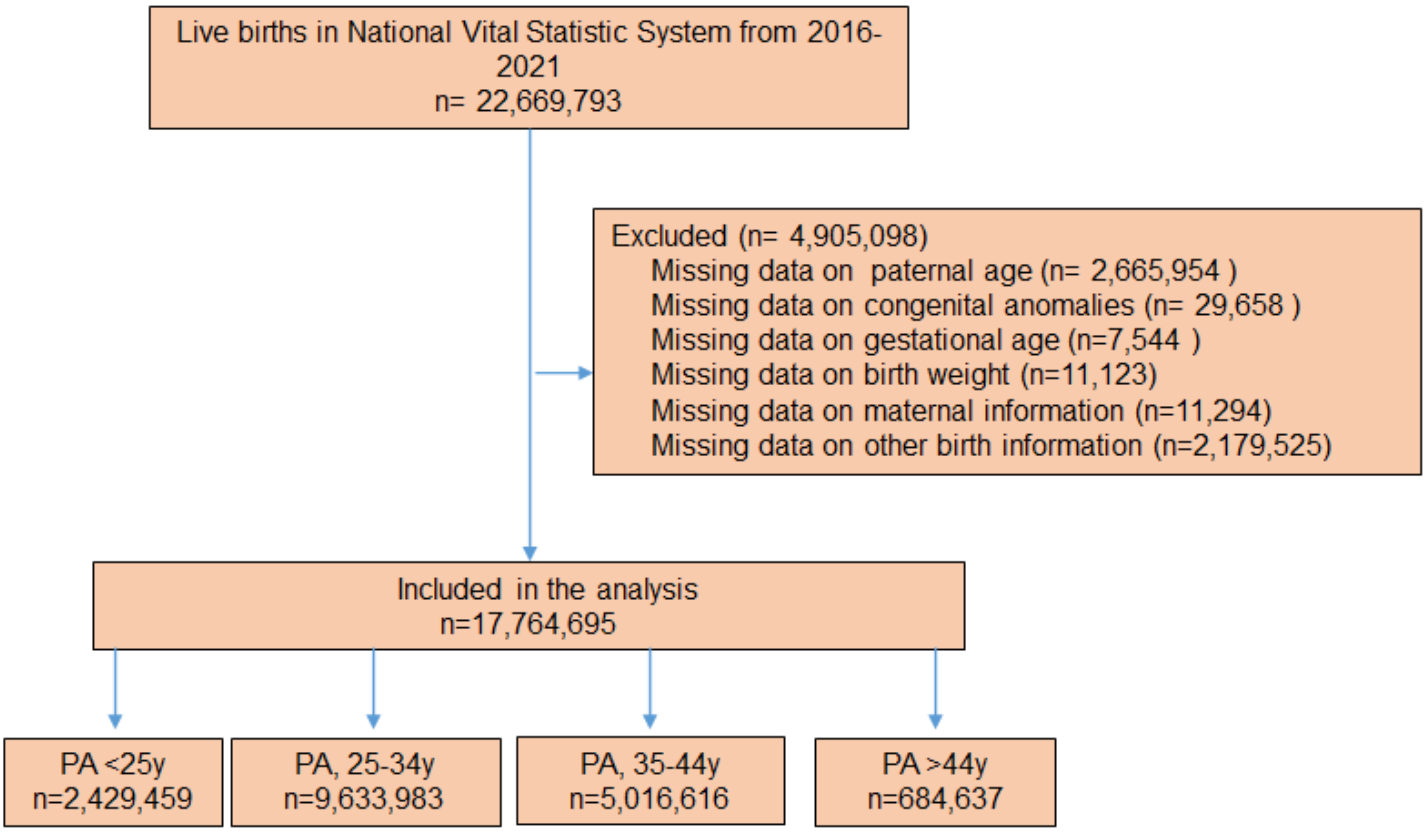

Figure 1

Participant Flowchart PA, paternal age