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Short Communication

Paternal age at birth and metabolic risk factors in adolescents: a nationwide survey

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ABSTRACT

Objective: The aim of the study is to examine associations between paternal age at childbirth and offspring cardiovascular risk factors in adolescence.
Study design: This is a cross-sectional study.
Methods: Data from the 2007–2016 Korea National Health and Nutrition Examination Survey was used. A total of 4,096 adolescents were included in the final analysis, and their information on blood pressure, fasting glucose level, and lipid profile was collected. Multiple linear regression models were applied to evaluate the effect of paternal age on cardiovascular risk factors with adjustment for potential confounders.
Results: The median age of participants was 13 years, and 53.2% were male. Maternal and paternal ages were closely correlated with each other, and older parents had older offspring. Paternal age was positively associated with levels of total cholesterol ($p = 0.033$) and triglycerides ($p = 0.042$) after adjusting for confounders.
Conclusion: This nationwide study shows that advanced paternal age is associated with a less favorable lipid profile in a dose-dependent manner.

Introduction

Among non-communicable diseases, cardiovascular (CV) disease is now the leading cause of mortality, but CV disease–related deaths are the most amenable to rapid change. Evidence that CV risk factors in childhood predict future CV risk is now irrefutable. Atherosclerosis begins in childhood and is associated with an unhealthy diet, genetic variations, and the presence of risk factors such as cigarette smoking, obesity, hypertension, diabetes mellitus, and dyslipidemia.[1] Emerging evidence from experimental[2] and epidemiologic[3] studies suggests that an impoverished prenatal environment due to advanced parental age can impact offspring health in later life beyond fetal growth restriction or prematurity.

There has been an increasing trend toward delayed parenthood, which shows no signs of abating. Although the influence of maternal age is more recognized than that of paternal age, postponed fatherhood also has potential consequences for offspring perinatal and childhood health.[3] Most

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studies of offspring health after delayed parenthood focus on the risk of obesity and provide inconclusive results. Much less attention has been paid to the relationship between delayed parenthood and other CV risk factors, especially those independent of obesity.

Evidence of the impact of paternal age at birth on offspring CV risk factors in childhood or adolescence is limited and conflicting. A large UK study reports no association between blood pressure at 15 years of age and maternal or paternal age,[4] whereas Savage et al. report that advanced paternal age at birth is associated with a less favorable lipid profile.[5] Here, we examined associations between paternal age at childbirth and offspring CV risk factors in adolescence.

Methods

We used nationwide data from the 2007–2016 Korea National Health and Nutrition Examination Survey (KNHANES), which is sampled based on stratified, multistage clustering methods. We identified 16,589 individuals with available data on both paternal and maternal age. Of these, we excluded 6057 individuals who were aged ≥19 years or who were ≤12 years younger than a parent and 6362 individuals who were aged ≤9 years, as they had no health examination data. We also excluded 74 individuals with a parent who had experienced a major vascular event, such as myocardial infarction, angina, or stroke. Therefore, a total of 4096 participants were included in the final analysis. All participants provided written informed consent to participate in the KNHANES. The KNHANES study followed the guidelines put forth in the Declaration of Helsinki. The present study protocol was approved by the Institutional Review Board of Gachon University Gil Medical Center (GFIRB 2019-042).

Our outcomes of interest were CV risk factors in adolescence including blood pressure, serum fasting glucose, total cholesterol, and triglycerides. For each CV risk factor, multiple linear regression models were applied to evaluate the effect of paternal age, with adjustment for potential confounders such as age, sex, body mass index (BMI), current household income, and maternal BMI and age. Household income was considered an indicator of socio-economic status. We included the current maternal BMI as a covariate to partly reflect the uterine environment at the time of pregnancy. As our participants were in a growth spurt period, older offspring were larger than younger offspring. Thus, we did not consider the BMI as a dependent variable but rather treated it as a confounder.

Studies examining the effect of paternal age must account for the influence of maternal age.[3] Pearson's correlation analysis was conducted to examine the correlation between paternal age and maternal age. Sensitivity analysis was also conducted to evaluate a potential confounding effect of maternal age. Maternal age was entered into the regression model as follows: in 1-year groups (main), in 2-year groups, and modeled using restricted cubic splines with knots at 25, 27, 29, 32, and 36 years. All analyses were performed using STATA SE 9.2 (Stata Corp., College Station, TX). All statistical tests were two-sided, and statistical significance was defined as a $P < 0.05$.

Results

The median age of participants was 13 years (interquartile range, 11–14 years), and 53.2% were men. The median parental age at birth was 29 years (range, 22–44 years) for mothers and 32 years (range, 23–57 years) for fathers. Maternal and paternal ages were closely correlated with each other (Pearson's correlation coefficient, 0.73; $P < 0.001$), and older parents had older offspring. The median values (interquartile ranges) of CV risk factors were as follows: systolic blood pressure, 105 mmHg (99–112 mmHg); diastolic blood pressure, 65 mmHg (60–70 mmHg); fasting glucose, 90 mg/dl (86–94 mg/dl); total cholesterol, 157 mg/dl (141–174 mg/dl); and triglycerides, 73 mg/dl (53–101 mg/dl). Table 1 shows some CV risk factors associated with paternal age at birth. Paternal age was positively associated with levels of total cholesterol ($P = 0.033$) and triglycerides ($P = 0.042$) after adjusting for age, sex, BMI, maternal BMI and age, and household income. Other approaches to adjustment for maternal age did not affect the estimates significantly: P-values were 0.022 for total cholesterol and 0.038 for triglycerides in 2-year groups; and 0.041 for total cholesterol and 0.063 for triglyceride in the model using restricted cubic splines.

Discussion

This nationwide study shows that advanced paternal age is associated with a less favorable lipid profile in a dose-dependent manner. Adolescent lipid profiles remain consistent or worsen in adulthood,[6] and thus, our finding suggests that offspring with older fathers at birth could be at a higher CV disease risk in adulthood. However, given that our test barely reached significance, the interpretation should be careful. In addition, clinical relevance is different from statistical significance, and it remains to be further elucidated.

Table 1 – Cardiovascular risk factors in adolescence associated with paternal age at birth.

Variables	Paternal age (per 1 year)		
	β	95% confidence interval	p[a]
Systolic blood pressure, mmHg	0.09	−0.02–0.20	0.121
Diastolic blood pressure, mmHg	0.04	−0.06–0.15	0.428
Fasting glucose, mg/dl	−0.06	−0.14–0.03	0.198
Total cholesterol, mg/dl	0.38	0.03–0.72	0.033
Triglyceride, mg/dl	0.68	0.03–1.34	0.042

BMI, body mass index.
[a] From the multiple regression model with adjustment for age (continuous), sex, BMI (continuous), maternal BMI (continuous) and age (continuous), and household income.

Advanced paternal age at conception, which is associated with greater total exposure to environmental toxins, is linked to the accumulation of *de novo* mutations and/or aberrant epigenetic modifications in germ cells.[7] Rates of genetic mutation in germ cells are expected to increase with age in fathers but not in mothers.[8] Non-biological factors including diet and/or physical activity might also underlie the association between paternal age and offspring CV risk factors. For example, compared with women, men have an earlier decline in physical activity by age at midlife,[9] which could impact on their offspring's physical activity.[10]

This study has the inherent limitations of all observational studies, and critical covariates such as diet and physical activity of both parents and offspring were also not assessed. In addition, our analysis lacked extensive information on obstetric and maternal characteristics at the time of pregnancy, including birth weight, birth order, breastfeeding, and the presence of complications such as pre-eclampsia or gestational diabetes, which might influence offspring outcomes. Nonetheless, the validity of our finding is increased by our large sample size, sample representativeness, and reliability of metabolic measures.

In conclusion, paternal age at birth is associated with increased serum lipid levels in Korean adolescents. Prospective studies are warranted to investigate possible triggers and underlying mechanisms. Further scrutiny is also required to determine whether our finding is replicable and whether paternal age remains an important CV risk factor when offspring reach adulthood.

Author statements

Ethical approval

The present study was approved by the Institutional Review Board of Gachon University Gil Medical Center (GFIRB 2019-042).

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Competing interests

None declared.

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