# Advanced Paternal Age With Risk of Lifespan in Male Offspring Using Chinese Genealogical Data

**yanyan xiong**
Hunan Normal University
**Xueqin Zhu**
Hunan Normal University
**Ying Xie** ( xieying@hunnu.edu.cn )
Hunan Normal University https://orcid.org/0000-0001-7568-2569

**Research**

**Keywords:** lifespan, Ding, paternal age, male offspring survival, genealogy data

**Posted Date:** September 14th, 2021

**DOI:** https://doi.org/10.21203/rs.3.rs-855933/v1

# Abstract

### Background

Advanced paternal age has been associated with a variety of adverse reproductive outcomes. However, the effects of paternal age on offspring lifespan are still controversial.

### Result

Here, we studied the correlation between parental reproductive age and offspring lifespan using a Chinese specific genealogy data. We chose a “Ding” genealogy data across 130 years during the Qing Dynasty (1726-1855). The present study showed that fathers aged more than 35 years were more likely to have male offspring with lower lifetime compared with fathers aged 20-35 years. The significant negative correlation between paternal age and male offspring lifespan existed after adjusted for maternal age. We proposed a new evidence that advanced paternal age is a risk for male offspring survival.


# Introduction

The average age of childbearing is increasing due to education, employment and marriage problems over the last decade. And the progress of assisted reproductive techniques increased the chance of older parents to conceive children, however, offspring with older parents are more likely to suffer healthy problems (Sharma et al., 2015).

Advanced maternal age has long been recognized as a risk factor for children's health. The quality of the intra-uterine environment may decline and the risk of neural tube defects and aneuploid (particularly Down syndrome) increases with maternal age (Pariente et al., 2019). Therefore, women over 35 years have a higher risk of spontaneous abortion and perinatal complications(Mehari et al., 2020, Pinheiro et al., 2019).

Increasing paternal age has also been shown to be associated with adverse reproductive outcomes on their offspring. Fathers aged more than 45 increased the risk of spontaneous abortion, premature birth and low birth weight after meticulous adjustment for maternal age (Nybo Andersen & Urhoj, 2017, Khandwala et al., 2018). Urhoj et al showed a significant increased risk of stillbirth when offspring of fathers aged 40 years or more in an analysis covering nearly 1 million Denmark pregnancies(Urhoj et al., 2017). Advanced parental age to one’s birth has also been identified with higher risks of numerous disorders, such as malignant cancer(Lu et al., 2010, Johnson et al., 2009), neuropsychiatric diseases(Khachadourian et al., 2021, Janecka et al., 2017), cardiovascular diseases(Savage et al., 2014, Eriksen et al., 2013) and other diseases compared with younger fathers.

However, the effects of paternal age on offspring lifespan are still controversial. Arslan showed minuscule paternal age effects on offspring survival(Arslan et al., 2017). Carslake et al found that adult survival improved in the offspring of older parents. Individuals have children at older ages tend to provide

their children a wealthier life, which may compensate for their physiological disadvantages (Carslake et al., 2019). Although older father's children would be less likely to survive based on evolutionary genetic theory, the lifelong consequences of parental age for the offspring are harder to evaluate due to the interference of confounding factors, such as medical level and socioeconomic status.

In this study, it is first known to analyze the relationship between paternal age and offspring lifespan with a Chinese characteristic genealogy data. The "Ding" database recorded male offspring information between 1726–1855. All the family members lived in the same region and had a similar lifestyle, socioeconomic status, education level and blood relationship. Especially the impact of health service on life expectancy was less than that in modern society, because medical care was generally backward in ancient times. The results suggested that advanced paternal age at birth may be a health risk for offspring life expectance.

# Methods

### Database

we searched genealogy data in the National Digital Library of China, and selected a relatively complete Ding family tree data living in Hefei City, Anhui Province during the Qing Dynasty (1726–1855). The paternal reproductive age, maternal reproductive age and offspring lifespan according to their documented birth time and death time are calculated.

### Data analysis

SPSS20.0 and GraphPad Prism 8.4 (GraphPad Software, Inc) were used to carry out statistical analysis. The relationship between paternal reproductive age and offspring lifespan was analyzed by LSD-t test of one-way ANOVA, simple linear correlation analysis and linear regression analysis. $P < 0.05$ was considered statistically significant.

# Results

### Basic information of "Ding" genealogy data.

The selected family tree involved four generations with 1,236 people in 130 years. Table 1 shows basic information on genealogy, including average and range of values for paternal reproductive age, maternal reproductive age and offspring life of data in this study. The paternal reproductive age range was 16–63 years, the maternal reproductive age range of 13–55 years and the offspring lifespan range of 2–95 years. The collected data at different age ranges and the mean of their offspring are shown in Table 2.

Table 1
Basic information of Ding genealogy data

| | Min | Max | Mean ± SD | N |
|---|---|---|---|---|
| Offspring birth year | 1726 | 1855 | 1780 ± 25.85 | 1236 |
| Paternal reproductive age | 16 | 63 | 33.48 ± 8.69 | |
| Maternal reproductive age | 13 | 55 | 28.22 ± 7.07 | |
| Offspring lifespan | 2 | 95 | 53.91 ± 17.66 | |

In order to exclude the influence of maternal reproductive age, we divided samples into different subgroups according to maternal reproductive age, as shown in Table 2.

Table 2
Offspring lifespan with paternal and maternal reproductive age

| Maternal reproductive age | Paternal reproductive age | N | Offspring lifespan |
|---|---|---|---|
| < 19 | < 20 | 9 | 52.56 ± 16.11 |
| | 20–35 | 72 | 57.11 ± 15.33 |
| | > 35 | 3 | 55.33 ± 19.42 |
| 19–35 | < 20 | 25 | 49.88 ± 21.35 |
| | 20–35 | 646 | 54.74 ± 17.55 |
| | > 35 | 295 | 52.88 ± 16.95 |
| > 35 | 20–35 | 6 | 55.17 ± 18.92 |
| | > 35 | 180 | 51.91 ± 19.39 |
| Total | | 1236 | 53.91 ± 17. |

**Correlation analysis between parental reproductive age and male offspring lifespan.**

To explore whether there was a relationship between the parental reproductive age and the length of male offspring lifespan, then correlation was further carried out. The results showed that there was a significantly negative correlation between the paternal reproductive age and male offspring lifespan (correlation coefficient R=-0.08, $P < 0.01$), while there was no correlation between the lifespan of children and the maternal reproductive age (correlation coefficient R=-0.04, $P = 0.22$, Table 3).

Table 3
The correlation analysis between parental reproductive age and male offspring lifespan.

| | R | *P* | N |
|---|---|---|---|
| Paternal reproductive age | -0.08 | < 0.01** | 1236 |
| Maternal reproductive age | -0.04 | 0.22 | |
| ***P*< 0.01, a significant correlation at 0.01 level (bilateral). | | | |

After samples were divided into different subgroups according to maternal reproductive age, the negative correlations between paternal reproductive age and male offspring lifespan still existed when mothers were at a moderate reproductive age (19–35 years). The linear regression was described by Y=-0.1723*X+59.68, as shown in Fig.1.

**Advanced paternal age is a risk for male offspring lifespan.**

Further difference analysis was conducted on 19–35 subgroups of maternal reproductive age. The mean lifespan of offspring in younger fathers (less than 20) was smallest. Then offspring lifetimes had a significant downward trend with the increase of paternal reproductive age. Compared with groups 20–24 of paternal reproductive age, offspring lifespans in groups 35–39, 40–44 and ≥ 45 significantly decreased (Table 4 and Fig. 2).

Table 4
Effects of paternal age on offspring lifetimes in subgroup (maternal age 19–35 years)

| Paternal reproductive age | N | Mean ± SD | *P* |
|---|---|---|---|
| < 20 | 25 | 49.88 ± 21.35 | 0.06 |
| 20–24 | 139 | 56.86 ± 16.29 | |
| 25–29 | 212 | 54.99 ± 17.17 | 0.32 |
| 30–34 | 256 | 54.22 ± 18.57 | 0.15 |
| 35–39 | 179 | 52.91 ± 16.53 | 0.04* |
| 40–44 | 105 | 52.32 ± 16.32 | 0.04* |
| ≥ 45 | 50 | 51.14 ± 19.41 | 0.04* |
| Total | 966 | 54.05 ± 17.49 | |
| **P*< 0.05, compared with 20–24 group. | | | |

# Discussion

In our study, we find support for negative paternal age effects on offspring survival with “Ding” genealogy data. Having child early (less than 20) may be harmful, but no significant conclusions could be drawn possibly due to lack of enough samples. Paternal age effects are massively affected by maternal age, so we observed the negative correlation between paternal age and offspring lifespan in mother age subgroup (19–35 years). Generally, the lifespan of offspring decreased gradually with the increase of the paternal reproductive age, but no relationship was observed between the lifespan and the maternal reproductive age. Additionally, we found a negative correlation between the lifespan of children and their paternal reproductive age.

Although no obvious effects of paternal age on offspring survival were observed in the past study, there were strong evidence in animal studies that paternal age is a high risk for offspring longevity(García-Palomares et al., 2009). Xie et al found the lifespan of hybrid mice born to 120 week-old fathers was shorter than that of offspring born to young fathers due to epigenetic changes in sperm(Xie et al., 2018). And similar results have been obtained in zebra finch, that is, offspring from older parents have reduced lifespans(Noguera et al., 2018).

Accumulated chromosomal aberrations and mutations with age in male germ cells are thought to be responsible for the increased risk of certain conditions with older fathers. After a person over 34 years old, the total sperm count is the first to decrease. Then total sperm concentration, percentage of sperm with normal morphology, semen volume, vitality of spermatozoa declined with increasing paternal age(Sharma et al., 2015, Brahem et al., 2011). Meanwhile, increased paternal age also affects epigenetics changes, DNA mutations, chromosomal aneuploidies and telomere length. The offspring mice of older fathers exhibited brain DNA methylation in regions associated with transcriptional regulation(Milekic et al., 2015). Jenkins et al identified 139 regions that are significantly hypomethylated with age in human sperm samples(Jenkins et al., 2014). Children of older fathers are probably more vulnerable to germline de novo point mutations (Kong et al., 2012). Moreover, aging-associated erosion of telomere length in old fathers could transferred to offspring, thus contributing to their premature aging phenotypes(Xie et al., 2018).

In modern society, increasing income and socioeconomic factors such as educational level and occupation with age are associated with many physical outcomes. Therefore, we chose the data from an ancient family tree to exclude the influence of modern medical technology and economic ability. The ancient family population had similar living environment, eating habits and blood relationship, which could reduce the influence of various confounding factors. Our study also has obvious defects, such as only male offspring data, limited information and lack of broad consideration of potential confounders.

The influence of the father is often overlooked because it is believed that the mother plays a dominant role in the reproductive process. The American College of Medical Genetics has defined advanced paternal age as 40 years or older at the time of conception(Toriello & Meck, 2008). In our study, we find paternal reproductive age older than 35 years was a risk for offspring survival using Chinese characteristic genealogy data. The serious consequences caused by advanced paternal age should

arouse the attention of the whole society. Possible interventions might include health promotion advising people about the risk of delaying childbearing and encouraging couples to have children earlier rather than later.

# Abbreviations

**SD:**Standard Deviation

# Declarations

### Ethics declarations

Competing interests

The authors declare that they have no competing interests.


### Funding

The study was sponsored by Changsha Natural Science Foundation Project (45045) and Natural Science Foundation of Hunan Province (2021JJ40374).


### Availability of data and materials

All data used during the study are available from the corresponding author by request.


### Author information

Yanyan Xiong, Xueqin Zhu and Ying Xie contributed to this work.

Affiliations

Key Laboratory of Molecular Epidemiology of Hunan Province, School of Medicine, Hunan Normal University, Changsha, 410081, P. R. China

Yanyan Xiong, Xueqin Zhu  Ying Xie


Contributions

XY performed the study and wrote the manuscript. XYY and ZX analyzed the data. XY and XYY approved the final manuscript. All the authors contributed to the article and approved the submitted version.


Corresponding authors

Correspondence to Ying Xie.



### Acknowledgements

Thanks to all authors for our contributions to this article.

# References


1. Arslan RC, Willfuhr KP, Frans EMet al. 2017. Older fathers' children have lower evolutionary fitness across four centuries and in four populations. *Proc Biol Sci* 284.
2. Brahem S, Mehdi M, Elghezal H, Saad.et al. The effects of male aging on semen quality, sperm DNA fragmentation and chromosomal abnormalities in an infertile population. J Assist Reprod Genet. 2011;28:425–32.
3. Carslake D, Tynelius P, van den Berg GJ. & Davey Smith.et al. 2019. Associations of parental age with offspring all-cause and cause-specific adult mortality. *Sci Rep* 9: 17097.
4. Eriksen W, Sundet JM, Tambs K. Paternal age at birth and the risk of obesity in young adulthood: a register-based birth cohort study of Norwegian males. Am J Hum Biol. 2013;25:29–34.
5. García-Palomares S, Navarro S, Pertusa JFet al. Delayed fatherhood in mice decreases reproductive fitness and longevity of offspring. Biol Reprod. 2009;80:343–9.
6. Janecka M, Mill J, Basson MAet al. Advanced paternal age effects in neurodevelopmental disorders-review of potential underlying mechanisms. Transl Psychiatry. 2017;7:e1019.
7. Jenkins TG, Aston KI, Pflueger Cet al. Age-associated sperm DNA methylation alterations: possible implications in offspring disease susceptibility. PLoS Genet. 2014;10:e1004458.
8. Johnson KJ, Carozza SE, Chow EJet al. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology. 2009;20:475–83.
9. Khachadourian V, Zaks N, Lin Eet al. Advanced paternal age and risk of schizophrenia in offspring - Review of epidemiological findings and potential mechanisms. Schizophr Res. 2021;233:72–9.
10. Khandwala YS, Baker VL, Shaw GMet al. Association of paternal age with perinatal outcomes between 2007 and 2016 in the United States: population based cohort study. BMJ. 2018;363:k4372.
11. Kong A, Frigge ML, Masson Get al. Rate of de novo mutations and the importance of father's age to disease risk. Nature. 2012;488:471–5.
12. Lu Y, Ma H, Sullivan-Halley Jet al. Parents' ages at birth and risk of adult-onset hematologic malignancies among female teachers in California. Am J Epidemiol. 2010;171:1262–9.
13. Mehari MA, Maeruf H, Robles CCet al. Advanced maternal age pregnancy and its adverse obstetrical and perinatal outcomes in Ayder comprehensive specialized hospital, Northern Ethiopia, 2017: a comparative cross-sectional study. BMC Pregnancy Childbirth. 2020;20:60.
14. Milekic MH, Xin Y, O'Donnell Aet al. Age-related sperm DNA methylation changes are transmitted to offspring and associated with abnormal behavior and dysregulated gene expression. Mol Psychiatry. 2015;20:995–1001.
15. Noguera JC, Metcalfe NB, Monaghan P. 2018. Experimental demonstration that offspring fathered by old males have shorter telomeres and reduced lifespans. *Proceedings of the Royal Society B: Biological Sciences* **285**.

16. Nybo Andersen AM, Urhoj SK. Is advanced paternal age a health risk for the offspring? Fertil Steril. 2017;107:312–8.
17. Pariente G, Wainstock T, Walfisch Aet al. Advanced Maternal Age and the Future Health of the Offspring. Fetal Diagn Ther. 2019;46:139–46.
18. Pinheiro RL, Areia AL, Mota Pinto A, Donato.et al. Advanced Maternal Age: Adverse Outcomes of Pregnancy, A Meta-Analysis. Acta Med Port. 2019;32:219–26.
19. Savage T, Derraik JG, Miles HLet al. Increasing paternal age at childbirth is associated with taller stature and less favourable lipid profiles in their children. Clin Endocrinol (Oxf). 2014;80:253–60.
20. Sharma R, Agarwal A, Rohra VKet al. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. Reprod Biol Endocrinol. 2015;13:35.
21. Toriello HV, Meck JM. Statement on guidance for genetic counseling in advanced paternal age. Genet Med. 2008;10:457–60.
22. Urhoj SK, Andersen PK, Mortensen LHet al. Advanced paternal age and stillbirth rate: a nationwide register-based cohort study of 944,031 pregnancies in Denmark. Eur J Epidemiol. 2017;32:227–34.
23. Xie K, Ryan DP, Pearson BLet al. Epigenetic alterations in longevity regulators, reduced life span, and exacerbated aging-related pathology in old father offspring mice. Proc Natl Acad Sci U S A. 2018;115:E2348–57.

# Figures

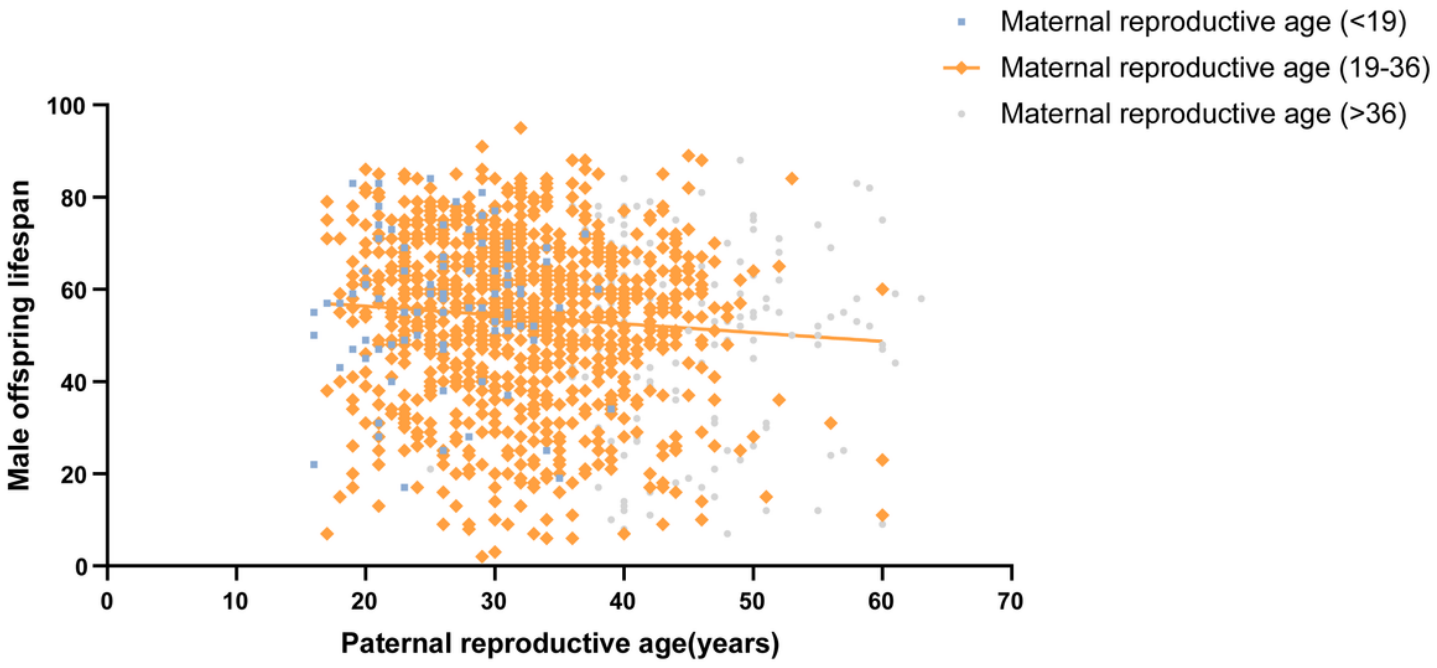


Figure 1

Paternal reproductive age dynamics with male offspring lifespan after stratified by maternal reproductive age.

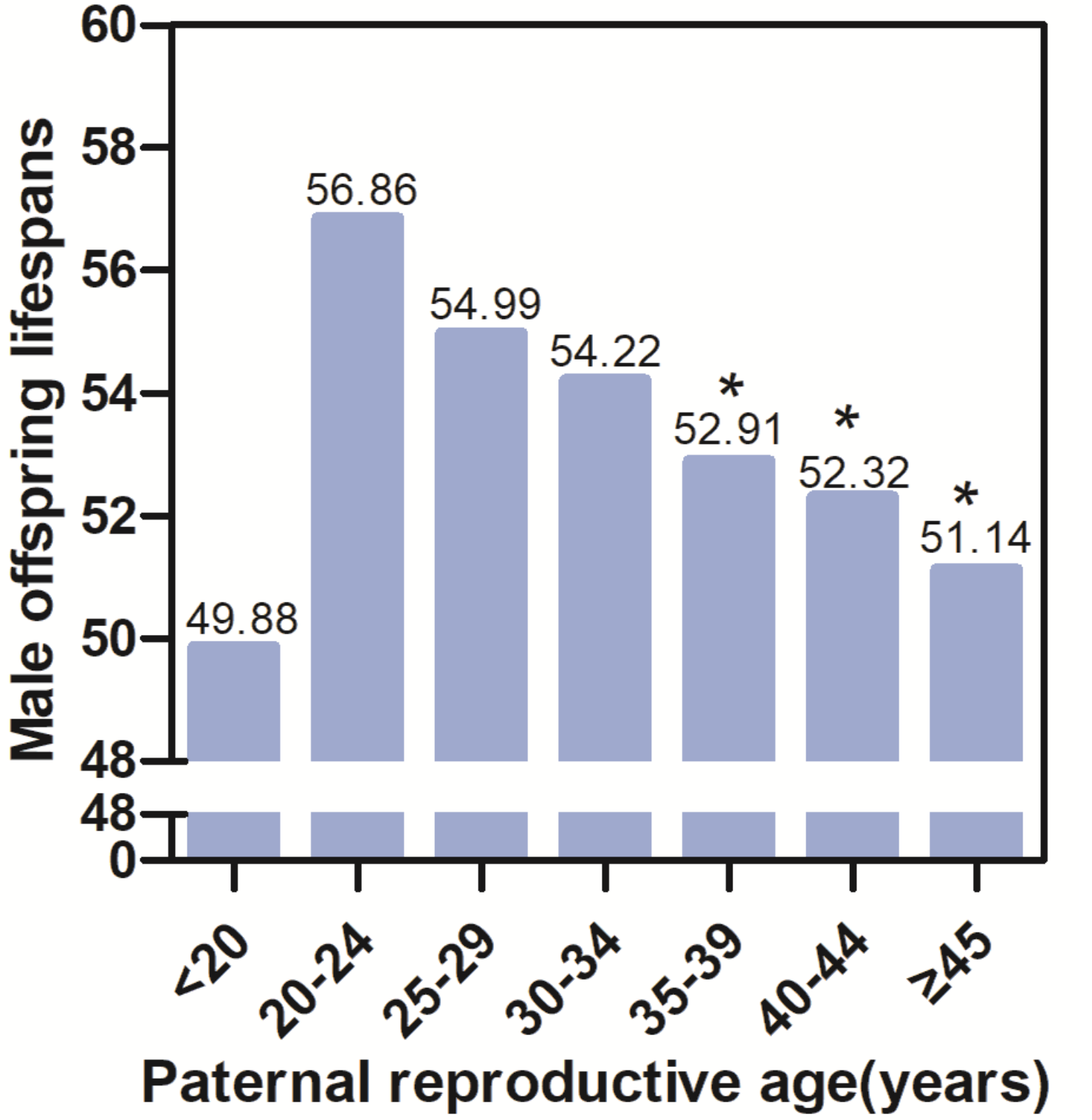


**Figure 2**

Effects of paternal age on offspring lifetimes in subgroup (maternal age 19-35 years) *P<0.05, compared with 20-24years.