Eur J Epidemiol (2008) 23:443–447
DOI 10.1007/s10654-008-9253-3

MORTALITY

Paternal age and mortality in children

Jin Liang Zhu · Mogens Vestergaard · Kreesten M. Madsen · Jørn Olsen

Received: 21 June 2007 / Accepted: 9 April 2008 / Published online: 25 April 2008

Abstract *Background* Since paternal age correlates with some diseases that have a high case-fatality, a paternal age effect on offspring's survival is expected but unsettled. We examined the association between paternal age and mortality in children in a large population-based cohort taking maternal age and socioeconomic factors into account. *Methods* From the Danish Fertility Database (1980–1996), we identified 102,879 couples and their firstborn singleton children. Information on childhood death ($N = 831$) was obtained by linking the cohort to the nationwide register on cause of death (1980–1998). *Results* We observed a U-shaped association between paternal age and the overall mortality rate in children up to 18 years of age. Adjustment for maternal age and other confounders reduced the mortality rate ratio (MRR) for children of younger fathers but not for children of older fathers. Compared with children of fathers aged between 25 and 29 years, the adjusted MRR was 1.77 (95% confidence interval 1.28–2.45) for children of fathers aged between 45 and 49 years and 1.59 (1.03–2.46) for children of fathers aged 50 years or more. The cause-specific MRRs were highest for congenital malformations [2.35 (1.42–3.88)] and injury or poisoning [3.43 (1.49–7.92)] for children of fathers aged 45 years or more. *Conclusion* Our data revealed a higher mortality in offspring of fathers aged 45 years or more that lasted into adulthood. This adds to the cumulating evidence on adverse effects of advanced paternal age in procreation.

Keywords Epidemiology · Mortality · Paternal age

Abbreviations

CI	Confidence interval
ICD8	The 8th Revision of International Classification of Diseases
ICD10	The 10th Revision of International Classification of Diseases
MRR	Mortality rate ratio

Introduction

Advanced paternal age has been associated with a higher risk of spontaneous abortions [9, 15, 24], stillbirth [1, 19], preterm birth [2, 30], congenital malformations [25, 28, 31], childhood cancer [10, 29], epilepsy [26], autism [17, 21], and schizophrenia [18, 23] in the offspring. The biological mechanisms behind these associations are unknown but may be related to de novo mutations and epigenetic changes in male germ cells with short and long term health consequences for the offspring. Males are responsible for the majority of new mutations in the human gene pool due to the constantly dividing reproductive stem cells, and the number of mutations increases significantly with age [6, 7]. If some of these mutations play a role for the diseases related to an advanced paternal age they may also have

J. L. Zhu (✉) · M. Vestergaard · K. M. Madsen
The Danish Epidemiology Science Centre, University of Aarhus, Vennelyst Boulevard 6, 8000 Aarhus C, Denmark
e-mail: zjl@soci.au.dk

M. Vestergaard
Department of General Practice, Institute of Public Health, University of Aarhus, Vennelyst Boulevard 6, 8000 Aarhus C, Denmark

J. Olsen
Department of Epidemiology, School of Public Health, UCLA, Box 951772, Los Angeles, CA 90095-1772, USA

profound effects on survival in childhood, but previous studies are scanty and conflicting [3, 5, 27].

We used nationwide registers in Denmark to evaluate the association between paternal age and mortality in children taking potential confounders like maternal age and socioeconomic factors into account.

Methods

This study is based on data from the Danish Fertility Database [16] that holds information on all individuals in Denmark older than 11 years and is updated annually with information on socioeconomic status, pregnancy outcome and family structure. From the Danish Fertility Database (1980–1996), we identified four cohorts of couples who had their first child. The first cohort consisted of all couples where both partners were older than 35 years at the time of the birth of the child ($N = 20{,}606$); the second cohort consisted of all couples where the man was older than 35 years and the woman was younger than 30 years ($N = 30{,}987$); the third cohort consisted of all couples where the man was younger than 30 years and the woman was older than 35 years ($N = 3{,}189$); and the fourth cohort consisted of a random sample of couples where both partners were younger than 30 years ($N = 50{,}000$). We constructed these four cohorts to obtain as large age variation between parents as possible. Only the couple's first child was included, but the mother and the father could be included in the cohort more than once with a different partner ($N = 1{,}749$ (1.7%) for mothers, and $N = 1755$ (1.7%) for fathers). We excluded adopted children ($N = 454$) and children of multiple births ($N = 1{,}449$), leaving a total of 102,879 singletons available for analyses.

Information on death was obtained by linking the children to the Register of Causes of Death [14] using the unique civil registration number assigned to all children at birth in Denmark. Up to three causes of death were recorded in this register, using the 8th Revision of International Classification of Diseases (ICD8) before 1994 and the 10th Revision of International Classification of Diseases (ICD10) since 1994. We classified causes of death into five groups (perinatal conditions, congenital malformation, ill-defined causes, injury and poisoning, and other diseases) according to the European short-list for causes of death (http://www.nom-nos.dk/Nomstats/European%20shortlist.doc). The classification was made prior to the analyses and depended on the number of expected death (calculated by the total number of death and the distribution of paternal age). We included a category if we expected at least five deaths in children of fathers older than 45 years.

Paternal age was categorized into seven age groups of 15–19, 20–24, 25–29, 35–39, 40–44, 45–49 and 50+ years, with the group of 25–29 years serving as a reference group. We collapsed two paternal age groups at both ends for analyses on causes of death due to small numbers. In the analyses, we included the following potential confounders: maternal age (in years), maternal parity (1, 2+) based upon previous live and still births, maternal education (<9, 9–11, >11 years) and income (quartiles), paternal education (<9, 9–11, >11 years) and income (quartiles), parental countries of origin (both parents from Denmark, at least one parent from other country), and calendar year (1980–1988, 1989–1996).

To evaluate the association between paternal age and overall mortality in children, we calculated mortality rate ratio (MRR) with 95% confidence interval (CI) by using Cox regression in STATA 9.1 (StataCorp, College Station, Texas, USA). The cohort members were followed from birth until time of death, emigration, or the end of follow-up (31 December 1998), whichever came first. Information on emigration was obtained from the Civil Registration System. To obtain a better fit of the model, we included linear and quadratic terms of maternal age, together with all the above potential confounders in the model. We also analysed the data according to age at death (infant death: <1 year of age; childhood death: 1–18 years of age) and causes of death. We examined the possible trend between paternal age and mortality in children by including only fathers aged 25 years or more and including paternal age in years as a continuous variable in the models. We further examined whether adverse pregnancy outcomes could explain the association between paternal age and mortality by restricting our analyses to children with a birth weight ≥2,500 g, gestational age ≥37 weeks, Apgar score = 10, and no congenital malformations.

Results

We followed 102,879 live-born singletons for up to 18 years (median 9.5 years) and identified 831 deaths, including 601 (72.3%) deaths in children younger than one year of age.

Children of younger fathers (<25 years) and older fathers (45+ years) had a higher overall mortality rate compared with children of fathers 25–29 years of age (Table 1). Adjustment for maternal age and other potential confounders reduced the mortality rate ratio for children of younger fathers, but the mortality rate ratio remained largely unchanged for children of fathers aged 45 years or more.

We saw a similar pattern for deaths before 1 year of age and for deaths during childhood between 1 and 18 years of age (Table 2).

Table 1 Mortality rate ratio (MRR) in children according to paternal age

Paternal age (years)	No. of children	No. of deaths	Mortality rate (1/1,000)	Crude MRR	Adjusted MRR	95% CI[a]	
15–19	1289	16	1.15	1.79	1.06	0.62	1.83
20–24	16688	175	0.96	1.51	1.22	0.99	1.51
25–29	34462	236	0.69	1.00	1.00	Reference	
35–39	31670	238	0.79	1.11	1.15	0.95	1.39
40–44	12243	88	0.78	1.06	1.09	0.84	1.43
45–49	4467	52	1.35	1.74	1.77	1.28	2.45
50+	2060	26	1.41	1.88	1.59	1.03	2.46
Test for trend					$P = 0.005$		

Cox regression; adjusted for maternal age and parity, parental education and income, parental countries of origin, and calendar year

[a] CI: Confidence interval

Table 2 Infant and child mortality rate ratio (MRR) according to paternal age

Paternal age (years)	No. of deaths	Mortality rate (1/1,000)	Crude MRR	Adjusted MRR	95% CI[a]	
Infant (<1 year)						
15–19	15	11.81	2.39	1.56	0.88	2.79
20–24	121	7.33	1.49	1.27	0.98	1.63
25–29	168	4.92	1.00	1.00	Reference	
35–39	181	5.78	1.17	1.18	0.94	1.47
40–44	61	5.04	1.02	0.99	0.72	1.36
45–49	33	7.48	1.52	1.44	0.97	2.16
50+	22	10.90	2.20	1.66	1.02	2.69
Test for trend				$P = 0.064$		
Child (1–18 years)						
15–19	1	0.08	0.37	0.18	0.02	1.35
20–24	54	0.33	1.54	1.12	0.76	1.66
25–29	68	0.22	1.00	1.00	Reference	
35–39	57	0.21	0.94	1.07	0.73	1.56
40–44	27	0.27	1.17	1.38	0.85	2.24
45–49	19	0.56	2.34	2.82	1.62	4.93
50+	4	0.24	1.05	1.21	0.43	3.42
Test for trend				$P = 0.027$		

Cox regression; adjusted for maternal age and parity, parental education and income, parental countries of origin, and calendar year

[a] CI: Confidence interval

We found an association of paternal age with deaths due to congenital malformations and deaths due to injury or poisoning (Table 3).

Restricting our analyses to children ($N = 79{,}704$) with birth weight ≥2,500 g, gestational age ≥37 weeks, Apgar score = 10, and no congenital malformations revealed similar results (data not shown).

Discussion

The association between paternal age and overall mortality rate in children up to 18 years of age was U-shaped. While the left side of the curve could be explained by young age of the mothers [12] and adverse socioeconomic factors, the association with advanced paternal age may have underlying biological causes or be related to differences in unadjusted lifestyle factors. The association was not explained by adverse pregnancy outcomes such as congenital malformations, low birth weight, preterm birth, and low Apgar score.

Denmark has a rather homogenous population. Most health services are free of charge for all residents, and it is unlikely that the associations we presented are due to age-related differences in access to health care. We had a large sample size with a large parental age variation, a virtually complete follow-up, and information on parental socioeconomic factors. Information on parental age and mortality are known to have very high quality [20], but causes of death is based upon information in the death certificates that sometimes are incomplete [14]. However, we have no reason to believe that the quality of the data

Table 3 Cause-specific mortality rate ratio (MRR) according to paternal age[a]

Paternal age (years)	No. of deaths	Mortality rate (1/1,000)	Crude MRR	Adjusted MRR	95% CI[b]	
Perinatal conditions (ICD10: P00-P96, ICD8: 760–779)[c]						
15–24	47	0.24	1.27	1.17	0.77	1.76
25–29	71	0.21	1.00	1.00	Reference	
35–39	71	0.24	1.09	1.00	0.70	1.42
40–44	24	0.21	0.95	0.78	0.47	1.29
45+	23	0.40	1.71	1.23	0.72	2.11
Test for trend				$P = 0.75$		
Congenital malformations (ICD10: Q00-Q99, ICD8: 740–759)[c]						
15–24	47	0.24	1.32	1.15	0.76	1.74
25–29	68	0.20	1.00	1.00	Reference	
35–39	69	0.23	1.11	1.23	0.86	1.76
40–44	28	0.25	1.16	1.36	0.84	2.19
45+	28	0.49	2.19	2.35	1.42	3.88
Test for trend				$P = 0.011$		
Ill-defined causes (ICD10: R00-R99, ICD8: 780–782.3, 782.5–791, 793–796)[c]						
15–24	34	0.17	2.71	1.55	0.87	2.77
25–29	24	0.07	1.00	1.00	Reference	
35–39	33	0.11	1.50	1.67	0.95	2.91
40–44	12	0.11	1.41	1.57	0.74	3.33
45+	5	0.09	1.11	1.16	0.41	3.24
Test for trend				$P = 0.26$		
Injury and poisoning (ICD10: V01-Y89, ICD8: E800-E999)[c]						
15–24	21	0.11	1.71	1.02	0.53	1.97
25–29	22	0.06	1.00	1.00	Reference	
35–39	22	0.07	1.12	1.34	0.71	2.52
40–44	10	0.09	1.35	1.71	0.76	3.83
45+	10	0.18	2.61	3.43	1.49	7.92
Test for trend				$P = 0.042$		
Other diseases (ICD10: A00-O99, ICD8: 000–738, 782.4, 792)[c]						
15–24	40	0.20	1.50	1.33	0.83	2.13
25–29	49	0.14	1.00	1.00	Reference	
35–39	41	0.14	0.93	0.89	0.57	1.38
40–44	14	0.12	0.83	0.78	0.41	1.48
45+	11	0.19	1.25	1.16	0.57	2.38
Test for trend				$P = 0.99$		

Cox regression; adjusted for maternal age and parity, parental education and income, parental countries of origin, and calendar year

[a] Seven cases had no diagnoses on cause of death

[b] CI: Confidence interval

[c] ICD10: The 10th Revision of International Classification of Diseases; ICD8: the 8th Revision of International Classification of Diseases

depends on the age of the father. Any misclassification may therefore bias the results towards lower estimates.

We know of only few studies that have examined the association between paternal age and mortality in young children [3, 5, 27]. One study found a higher mortality in offspring of older fathers [27], whereas two found no paternal age effect. None of the studies took causes of death into account, but they were performed in developing countries where the infectious diseases and malnutrition are the predominant causes of death.

We found an association between paternal age and deaths due to congenital malformations, the leading cause of death in our study population. This result is in line with previous studies showing an association between advanced paternal age and some congenital malformations [6, 25, 28, 31]. Several studies have also shown that fetal death correlates with paternal age [1, 9, 15, 19, 24].

Advanced age is expected to correlate with diseases related to subfecundity that could fully or partly explain the association we found. Subfecundity is more prevalent among older first-time parents either as a result of an age-related fecundity or selection, since fertile couples often conceive at a younger age. Subfecundity has been associated with adverse pregnancy outcomes, including spontaneous abortion and perinatal mortality [11, 13]. Unfortunately, we had no information on fecundity.

We also found an association between paternal age and death caused by injury and poisoning, which has not been reported before. Although this finding may indicate that social and behavioral factors are not fully controlled for, children of older fathers may be more susceptible to accidents due to impaired development, impaired psychomotor skills or behaviour problems [8, 22].

Our results show that advanced paternal age is associated with an increased mortality in children. Our results and other findings [1, 2, 9, 10, 15, 17–19, 21, 23–26, 28–31] should be weighed up against socio-economic advantages for children born to older fathers [4].

Acknowledgement We thank Jørn Hansen Schmidt and Søren Leth-Sørensen for help with establishment of the cohorts. This study was supported by a grant from the Danish Medical Research Council (Grant No. 22-02-0363). The activities of the Danish Epidemiology Science Centre are financed by grants from the Danish National Research Foundation.

References

1. Astolfi P, De Pasquale A, Zonta LA. Late paternity and stillbirth risk. Hum Reprod. 2004;19:2497–501.
2. Astolfi P, De Pasquale A, Zonta LA. Paternal age and preterm birth in Italy, 1990 to 1998. Epidemiology. 2006;17:218–21.
3. Becher H, Muller O, Jahn A, Gbangou A, Kynast-Wolf G, Kouyate B. Risk factors of infant and child mortality in rural Burkina Faso. Bull World Health Organ. 2004;82:265–73.
4. Bray I, Gunnell D, Davey SG. Advanced paternal age: how old is too old? J Epidemiol Community Health. 2006;60:851–3.
5. Brittain AW. The effect of parental age, birth order and other variables on early childhood mortality: a Caribbean example. Soc Sci Med. 1992;35:1259–71.
6. Crow JF. The origins, patterns and implications of human spontaneous mutation. Nat Rev Genet. 2000;1:40–7.
7. Crow JF. Age and sex effects on human mutation rates: an old problem with new complexities. J Radiat Res (Tokyo). 2006;47(Suppl B):B75–82.
8. Day SM, Wu YW, Strauss DJ, Shavelle RM, Reynolds RJ. Causes of death in remote symptomatic epilepsy. Neurology. 2005;65:216–22.
9. De La RE, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. Hum Reprod. 2002;17:1649–56.
10. Dockerty JD, Draper G, Vincent T, Rowan SD, Bunch KJ. Case–control study of parental age, parity and socioeconomic level in relation to childhood cancers. Int J Epidemiol. 2001;30:1428–37.
11. Draper ES, Kurinczuk JJ, Abrams KR, Clarke M. Assessment of separate contributions to perinatal mortality of infertility history and treatment: a case–control analysis. Lancet. 1999;353:1746–9.
12. Gilbert W, Jandial D, Field N, Bigelow P, Danielsen B. Birth outcomes in teenage pregnancies. J Matern Fetal Neonatal Med. 2004;16:265–70.
13. Joffe M, Li Z. Association of time to pregnancy and the outcome of pregnancy. Fertil Steril. 1994;62:71–5.
14. Juel K, Helweg-Larsen K. The Danish registers of causes of death. Dan Med Bull. 1999;46:354–7.
15. Kleinhaus K, Perrin M, Friedlander Y, Paltiel O, Malaspina D, Harlap S. Paternal age and spontaneous abortion. Obstet Gynecol. 2006;108:369–77.
16. Knudsen LB. The Danish fertility database. Dan Med Bull. 1998;45:221–5.
17. Lauritsen MB, Pedersen CB, Mortensen PB. Effects of familial risk factors and place of birth on the risk of autism: a nationwide register-based study. J Child Psychol Psychiatry. 2005;46:963–71.
18. Malaspina D, Harlap S, Fennig S, Heiman D, Nahon D, Feldman D, Susser ES. Advancing paternal age and the risk of schizophrenia. Arch Gen Psychiatry. 2001;58:361–7.
19. Nybo Andersen AM, Hansen KD, Andersen PK, Davey SG. Advanced paternal age and risk of fetal death: a cohort study. Am J Epidemiol. 2004;160:1214–22.
20. Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish civil registration system. A cohort of eight million persons. Dan Med Bull. 2006;53:441–9.
21. Reichenberg A, Gross R, Weiser M, Bresnahan M, Silverman J, Harlap S, Rabinowitz J, Shulman C, Malaspina D, Lubin G, et al. Advancing paternal age and autism. Arch Gen Psychiatry. 2006;63:1026–32.
22. Shavelle RM, Strauss DJ, Pickett J. Causes of death in autism. J Autism Dev Disord. 2001;31:569–76.
23. Sipos A, Rasmussen F, Harrison G, Tynelius P, Lewis G, Leon DA, Gunnell D. Paternal age and schizophrenia: a population based cohort study. BMJ. 2004;329:1070.
24. Slama R, Bouyer J, Windham G, Fenster L, Werwatz A, Swan SH. Influence of paternal age on the risk of spontaneous abortion. Am J Epidemiol. 2005;161:816–23.
25. Stene J, Fischer G, Stene E, Mikkelsen M, Petersen E. Paternal age effect in Down's syndrome. Ann Hum Genet. 1977;40:299–306.
26. Vestergaard M, Mork A, Madsen KM, Olsen J. Paternal age and epilepsy in the offspring. Eur J Epidemiol. 2005;20:1003–5.
27. Wunsch G, Gourbin C. Parents' age at birth of their offspring and child survival. Soc Biol. 2002;49:174–84.
28. Yang Q, Wen SW, Leader A, Chen XK, Lipson J, Walker M. Paternal age and birth defects: how strong is the association? Hum Reprod. 2007;22:696–701.
29. Yip BH, Pawitan Y, Czene K. Parental age and risk of childhood cancers: a population-based cohort study from Sweden. Int J Epidemiol. 2006;35:1495–503.
30. Zhu JL, Madsen KM, Vestergaard M, Basso O, Olsen J. Paternal age and preterm birth. Epidemiology. 2005;16:259–62.
31. Zhu JL, Madsen KM, Vestergaard M, Olesen AV, Basso O, Olsen J. Paternal age and congenital malformations. Hum Reprod. 2005;20:3173–7.