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Parental age at delivery and a man's semen quality

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STUDY QUESTION: Is parental age at delivery associated with a man's semen quality?

SUMMARY ANSWER: In this large register-based study both mother's and father's age are found to have minimal effects on semen quality in men.

WHAT IS KNOWN ALREADY: Both maternal and paternal age have been associated with a range of adverse health effects in the offspring. Given the varied health effects of parental age upon offspring, and the sensitivity of genital development to external factors, it is plausible that the age of a man's mother and father at conception may impact his reproductive health. To our knowledge this is the first examination of the effects of parental age on semen quality.

STUDY DESIGN, SIZE, DURATION: A retrospective cohort study of 10 965 men with semen data and parental data.

PARTICIPANTS/MATERIALS, SETTING, METHODS: The study was based on Danish men referred to the Copenhagen Sperm Analysis Laboratory due to infertility in their partnership. Men born from 1960 and delivering a semen sample until year 2000 were included. The men were linked to the Danish Civil Registration System to obtain information on parent's age at delivery. Logistic regression analyses were used to calculate odds ratios and 95% confidence intervals for impaired semen quality. Linear regression analyses were used to examine a relationship between semen parameters and paternal age.

MAIN RESULTS AND THE ROLE OF CHANCE: There were no convincing effect of either mother's or father's age on a man's semen quality. As no trends were noted, the few statistically significant results are likely attributable to chance.

LIMITATIONS, REASONS FOR CAUTION: Information regarding individual subject characteristics which may impact sperm production (i.e. smoking, BMI) were not available. While our sample size was large, we cannot exclude the possibility that a trend may have been identified with a still larger sample. In addition, the Danish Civil Registration System is merely administrative and hence does not discriminate between biological and adopted children. However, the low rate of adoption (≈2%) suggests that misclassification would have a minimal impact. The men were all referred to the laboratory for infertility problems in their partnership and, therefore, do not represent the general population. We, however, compared semen quality among men within the cohort, and it is therefore less important whether they, in fact, represent the general population.

WIDER IMPLICATIONS OF THE FINDINGS: The current study found no link between parental age and a son's semen quality, suggesting other factors may explain recent impairments in men's reproductive health.

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Introduction

Over the past several decades, the age at which men and women begin families has increased in many countries (Lutz, 2006; Hvidtfeldt *et al.*, 2010; Martin *et al.*, 2011). For example, in 1980 the average age of women and men becoming parents in Denmark was 26.8 and 30.0 years, which increased to 30.3 and 33.0 years, respectively, by 2006 (Statistics Denmark, 2013). The etiology for delayed procreation has been postulated to result from biological and/or social reasons (Lutz, 2006; Lassen *et al.*, 2012). Regardless of the cause, there has been a concern regarding the effects of such demographic shifts upon the health of subsequent generations.

Increasing maternal age has been linked to intrauterine growth restriction, low birthweight, congenital malformations and perinatal mortality in offspring (Jacobsson *et al.*, 2004; Salem *et al.*, 2011). In addition, higher paternal age has been linked to a linear increase in germline mutations with a subsequent elevation in autism risk (Kong *et al.*, 2012). Moreover, investigators have linked paternal age, independent of maternal age, to higher risk of congenital anomalies, cancers, schizophrenia and impaired cognitive abilities in offspring (Goriely and Wilkie, 2012). Given the varied health effects of parental age upon offspring and the sensitivity of genital development to external factors, it is plausible that the age of a man's mother and father at conception may impact his reproductive health. Indeed, parental age has been shown to correlate with a man's risk of cryptorchidism and testis cancer (Moller and Skakkebaek, 1997; Cook *et al.*, 2008).

Studying the relationship between parental age and sperm production demands a large sample size and comprehensive data on the parental age at conception. The Copenhagen Sperm Analysis Laboratory has examined semen samples beginning in 1963 until present day, and the Danish Civil Registration System makes it possible to obtain information on parental age. Using this unique data set, we therefore studied the associations between parental age (both maternal and paternal) and subsequent semen quality.

Materials and Methods

Study population

For decades, men in the Copenhagen area have been referred to the Copenhagen Sperm Analysis Laboratory for semen analyses by general practitioners and urologists. The Laboratory is one of several public semen analysis laboratories in Denmark. The men are classified by physicians in the laboratory to the following diagnoses: vasectomy, infertility, azoospermia and other. Most of the men are referred due to infertility. As a couple's infertility may be attributed to male factor, female factor or a combination, men with normal and abnormal sperm production are represented. Volume, sperm concentration, total sperm count and percentages of morphologically abnormal and immotile spermatozoa were measured. The period of abstinence was recorded. The methods of semen analysis have not changed significantly during the period of sampling, and the analyses have in >40 years been supervised by the same laboratory technician. As some men delivered more than one semen sample, only the man's first semen sample was used. The methods used for semen analysis have been described previously (Bostofte *et al.*, 1982a,b; Bostofte *et al.*, 1984). Briefly, all specimens were analyzed within 1 h of ejaculation into a standard tube. Immediately after receipt, and not later than 2 h after ejaculation, the grade of motility was assessed by counting the motile and immotile spermatozoa using a light microscope with ×600 magnification. Through the unique Danish personal identification number [central person register (CPR)] the men were linked to the Danish Civil Registration System to determine parental identification. Only men born since 1960 were included as this birth year represents a cutoff from which the linkage between children and parents is nearly complete. Men referred to the Copenhagen Sperm Analysis Laboratory due to infertility from 1977 until year 2000 were included. Men with azoospermia were excluded from the analyses as vasectomy status could not be determined with certainty.

Data analysis

Logistic regression analysis was used to estimate adjusted odds ratios (OR) and 95% confidence intervals (CIs) for a man having abnormal semen parameters. Except for morphology, which was not assessed by strict criteria, abnormal semen parameters (semen volume <1.5 ml; sperm concentration <15 million/ml; total sperm count <39 million; immotile spermatozoa >60%; abnormal spermatozoa >50%) were defined based on World Health Organization (WHO) definitions of subfertility from 2010 (Cooper *et al.*, 2010; World Health Organization, 2010). Adjustments were done for birth cohort, birth order and maternal and paternal age, respectively. Age was examined both as a continuous (data not shown) and categorical variable (paternal age: <25, 25–30, 30–35, ≥35; maternal age: <25, 25–30, ≥30).

Linear regression models analyzed semen characteristics as continuous variables to estimate slopes. Given the nonparametric distribution of most semen parameters, a sensitivity analysis was performed after which the concentration, total sperm count and percent abnormal spermatozoa were square-root transformed and the percent of immotile spermatozoa was cubic-root transformed. No meaningful alterations in our conclusions were observed. Again, adjustments were done for birth cohort, birth order and maternal and paternal age. Student's *t*-test was used to test the slopes for significance, defined as $P < 0.05$.

All analyses were conducted with the SAS, version 9.1., software package (SAS institute, Inc., Cary, NC, USA).

Results

In all, 10 965 men were identified with semen data and linked data regarding parent's age at delivery. The man's mean age at semen analysis was 28.7 (± 3.8). The average age of the mother and father were 26.3 and 29.4 years, respectively. No differences based on maternal or paternal age were apparent based on semen volume, sperm concentration, total sperm count, sperm motility or sperm morphology (Table I).

After stratifying based on semen quality (referencing WHO 5th edition criteria; Cooper *et al.*, 2010; World Health Organization, 2010), 5.0% of men had low volume (<1.5 ml), 21.4% had low concentration (<15 million/ml), 19.4% had low total sperm count (<39 million), 5.7% had low sperm motility (≤60%) and 12.5% had low morphology (≤50%). Overall, no differences in the OR of impaired sperm quality based on maternal or paternal age were identified. Moreover, after controlling for the other parent's age and birth order, no significant trends were apparent. In addition, the analyses were repeated using the WHO 4th edition criteria (World Health Organization, 1999), with no meaningful changes in the conclusions.

While no trends were apparent overall, some individual differences based on age were noted. There was a higher odds of low volume and a borderline significant lower odds of oligospermia in sons born to mothers <25 years old compared with mothers aged 25–30 (OR 1.33, 95% CI 1.05–1.69 and OR 0.89, 95% CI 0.78–1.0; Table II). Fathers aged 30–35 had a lower odds of siring sons with oligospermia compared with younger fathers (OR 0.83, 95% CI 0.72–0.95).

Table I Semen parameters stratified by parental age, birth order and birth cohort (median and 5–95th percentile values listed).

	n	Concentration (million/ml)		Volume (ml)		Total count (million)		Morphology (% abnormal)		Motility (% immotile)	
		Median	5–95 PCTL	Median	5–95 PCTL	Median	5–95 PCTL	Median	5–95 PCTL	Median	5–95 PCTL
Paternal age at delivery											
<25	2 933	45.0	1.1–172.0	3.5	1.4–6.5	147.4	2.9–579.8	30	16–62	28	18–66
25–30	3 667	47.0	0.9–174.0	3.5	1.4–6.5	156.6	3.0–592.0	30	16–62	28	17–63
30–35	2 391	47.0	1.4–169.7	3.5	1.5–6.5	156.4	4.3–570.3	31	15–61	28	17–61
>35	1 974	45.0	1.1–168.0	3.5	1.4–6.6	150.5	3.2–547.5	30	15–62	28	18–66
Maternal age at delivery											
<25	5 108	46.0	1.2–172.1	3.5	1.4–6.5	153.6	3.6–580.0	30	16–61	28	17–64
25–30	3 361	46.0	0.9–168.0	3.5	1.5–6.5	156.0	2.7–577.5	30	15–62	28	18–63
>30	2 496	47.0	1.1–174.0	3.4	1.4–6.5	150.0	3.8–570.4	31	15–62	28	17–65
Birth order (based on mother)											
1	5 863	46.0	1.1–171.6	3.5	1.5–6.5	153.0	3.4–572.2	30	15–62	28	17–63
2	3 627	46.0	1.1–169.0	3.5	1.5–6.5	153.7	3.1–576.7	31	16–62	28	18–63
3+	1 475	46.0	1.0–179.0	3.4	1.3–6.5	154.0	3.2–586.4	30	15–60	28	17–68
Birth cohort											
1960–64	5 823	47.0	1.2–177.0	3.5	1.4–6.5	156.0	3.8–580.0	29	15–59	28	17–65
1965–69	3 792	45.0	1.0–168–0	3.5	1.5–6.5	151.8	2.9–585.9	31	15–64	28	17–63
1970–74	1 199	44.0	1.1–159.0	3.3	1.5–6.2	144.0	3.0–535.5	34	17–66	27	18–62
1975–79	148	35.5	0.4–157.0	3.4	1.4–6.4	127.3	1.3–549.0	37	19–66	28	17–60

In addition, linear models failed to identify any trends in the association between maternal or paternal age at delivery and a son's semen volume, sperm concentration, total sperm count, sperm motility or sperm morphology. However, a few individual analyses did suggest a possible relationship between parental age and semen quality. After adjustments, sons of the youngest father's had significantly lower sperm concentration and total sperm count and more immotile spermatozoa compared with sons of fathers aged 25–30, and the sons had fewer abnormal spermatozoa if the father was above 35 years of age. If the mother was either younger or older than the reference group aged 25–30, the sons had lower semen volume (Table III).

Discussion

The current report demonstrates that parental age and birth order have minimal effects on semen quality in men. We found no evidence for a linear association between parental age and semen quality. Similarly, no association was found between parental age and impairments in semen quality. To our knowledge this is the first examination of the effects of parental age on semen quality.

Other investigations have explored the role of parental age on men's reproductive health. The incidence of testis cancer in relation to maternal age has been extensively explored with heterogeneous results. Some investigations have found a relationship between a mother's age and her son's risk of testis cancer, while others have found no correlation (Moller and Skakkebaek, 1997; Petridou *et al.*, 1997; Dieckmann *et al.*, 2001; English *et al.*, 2003; Cook *et al.*, 2008). In fact, the most recent meta-analysis found no association (Cook *et al.*, 2009). In addition, a positive relationship was identified between maternal age and the risk of cryptorchidism (Moller and Skakkebaek, 1997). Given the relationship between testis cancer, cryptorchidism and spermatogenesis, a relationship between parental age and semen quality seemed plausible. Investigators have posited hormonal alterations with age, an accumulation of genetic mutations in sperm and eggs in aging parents, and environmental factors as possible culprits linking parental age to the reproductive health of the offspring (Moller and Skakkebaek, 1997; Ata *et al.*, 2012; Kong *et al.*, 2012).

As the age of conception is increasing in the industrialized world, the implications and causes of the trend have been debated (Lutz, 2006). With evidence of a decline in male reproductive health over the past several decades (e.g. declining semen quality, sex ratio and increasing testis cancer incidence), it is conceivable that delayed childbearing may play a role (Carlsen *et al.*, 1992; McGlynn *et al.*, 2003; Mathews and Hamilton, 2005; Rolland *et al.*, 2013). The current report found no link between parental age and a son's semen quality, suggesting other factors may explain recent impairments in men's reproductive health.

As various elements can affect spermatogenesis, to determine the impact of parental age on spermatogenesis requires both a large semen database as well as detailed information on parental age and birth order which have likely limited prior analyses. However, no trends were evident among both fathers and mothers making it unlikely that further stratified analyses would have modified our conclusions. This

Table II **Unadjusted and adjusted results from logistic regression analyses of semen quality by paternal and maternal age.**

	Volume		Concentration		Total sperm count		Motility		Morphology	
	OR volume <1.5 ml	**95% CI**	**OR concentration <15 million/ml**	**95% CI**	**OR <39 million**	**95% CI**	**OR > 60% immotile sp.**	**95% CI**	**OR > 50% abnormal sp.**	**95% CI**
Unadjusted results										
Paternal age at delivery										
<25	1.029	0.826; 1.283	1.039	0.923; 1.170	1.058	0.937; 1.196	1.176	0.954; 1.449	0.969	0.834; 1.125
25–30	Ref		Ref		Ref		Ref		Ref	
30–35	0.813	0.633; 1.044	0.948	0.835; 1.077	**0.876***	0.767; 1.002	0.953	0.755; 1.204	0.999	0.853; 1.169
≥35	1.079	0.845; 1.378	1.033	0.904; 1.180	1.051	0.915; 1.205	1.190	0.943; 1.503	0.971	0.820; 1.150
Maternal age at delivery										
<25	**1.344****	1.089; 1.657	0.946	0.850; 1.052	1.002	0.897; 1.119	1.062	0.877; 1.287	0.927	0.810; 1.060
25–30	Ref		Ref		Ref		Ref		Ref	
≥30	**1.292****	1.011; 1.653	0.980	0.864; 1.112	1.047	0.918; 1.193	1.134	0.907; 1.418	1.023	0.874; 1.197
Adjusted results										
Paternal age at delivery[a]										
<25	0.936	0.739; 1.185	1.093	0.961; 1.244	1.105	0.967; 1.263	1.210	0.963; 1.520	1.012	0.859; 1.193
25–30	Ref		Ref		Ref		Ref		Ref	
30–35	0.831	0.633; 1.091	0.916	0.798; 1.051	**0.833***	0.721; 0.964	0.904	0.702; 1.164	0.972	0.819; 1.154
≥35	1.035	0.756; 1.417	0.993	0.840; 1.173	0.967	0.813; 1.150	1.077	0.803; 1.445	0.933	0.756; 1.152
Maternal age at delivery[b]										
<25	**1.329****	1.045; 1.690	**0.886***	0.782; 1.004	0.911	0.800; 1.037	0.952	0.760; 1.193	0.915	0.782; 1.072
25–30	Ref		Ref		Ref		Ref		Ref	
≥30	1.245	0.934; 1.660	0.995	0.859; 1.153	1.074	0.920; 1.252	1.094	0.842; 1.422	1.118	0.930; 1.343

[a]Adjusted for maternal age, birth order and birth cohort.
[b]Adjusted for paternal age, birth order and birth cohort.
*$P < 0.10$; **$P < 0.05$

Table III Unadjusted and adjusted results from linear regression analyses of semen quality by paternal and maternal age.

	Volume		Concentration (square-root transformed)		Total sperm count (square-root transformed)		% immotile sp. (cubic transformed)		% abnormal sp. (square-root transformed)	
	β	*P*-value	*β*	*P*-value	*β*	*P*-value	*β*	*P*-value	*β*	*P*-value
Unadjusted results										
Paternal age at delivery										
<25	−0.053	0.178	−0.132	0.147	**−0.319***	0.057	**0.019***	**0.086**	−0.012	0.681
25–30	Ref		Ref		Ref		Ref		Ref	
30–35	0.014	0.729	−0.013	0.897	−0.019	0.913	0.0002	0.9885	0.009	0.789
≥35	−0.033	0.456	−0.143	0.163	**−0.355***	0.060	0.019	0.111	−0.049	0.146
Maternal age at delivery										
<25	**−0.110****	0.002	0.101	0.214	0.002	0.991	0.001	0.940	−0.019	0.489
25–30	Ref		Ref		Ref		Ref		Ref	
≥30	**−0.108****	0.009	0.056	0.561	−0.119	0.503	0.016	0.162	0.008	0.806
Adjusted results										
Paternal age at delivery[a]										
<25	−0.017	0.694	**−0.201****	0.041	**−0.383****	0.035	**0.025****	0.034	−0.002	0.953
25–30	Ref		Ref		Ref		Ref		Ref	
30–35	0.010	0.815	0.0004	0.973	0.012	0.949	−0.010	0.443	0.001	0.968
≥35	−0.009	0.870	−0.163	0.203	−0.329	0.162	0.002	0.894	**−0.062***	0.137
Maternal age at delivery[b]										
<25	**−0.101****	0.013	**0.180***	0.059	0.150	0.391	−0.013	0.246	−0.020	0.528
25–30	Ref		Ref		Ref		Ref		Ref	
≥30	**−0.111****	0.023	0.094	0.407	−0.042	0.839	0.016	0.242	**0.069***	0.062

[a]Adjusted for maternal age, birth order and birth cohort.
[b]Adjusted for paternal age, birth order and birth cohort.
*$P < 0.10$; **$P < 0.05$.

study has several advantages. It is large and it was possible to identify parents from Danish population registries. In addition, technicians in the laboratory used the same methods of analysis during the entire study period, reducing variation in semen analyses.

Several important limitations warrant mention. Information regarding individual subject characteristics that may impact sperm production (i.e. smoking, BMI) were not available. A relationship between parental age and lifestyle factors would confound the relationship; however, there is no indication of such an association. However, smoking has declined over the past several decades while the age of parents has increased (Clemmensen *et al.*, 2012). While our sample size was large, we cannot exclude the possibility that a trend may have been identified with a still larger sample. In addition, the Danish Civil Registration System is merely administrative and hence does not discriminate between biological and adopted children. However, the low rate of adoption (≈2%) suggests that misclassification would have a minimal impact (Statistics Denmark, 2013).

Another limitation to our study is that the men were all referred to the laboratory for infertility problems and, therefore, do not represent the general population. In fact, they had a lower mortality than the general population, suggesting that 'healthy selection' has been taking place (Jensen *et al.*, 2009). Socioeconomic factors are likely to have been important for referral patterns, especially in the early study period, when infertility treatment was not an integrated part of the established health-care system. Therefore, the men in our study may have parents with higher socioeconomic status than the general population and therefore may be a higher age at child birth. We, however, compared semen quality among men within the cohort, and it is therefore less important whether they, in fact, represent the general population. In addition, socioeconomic status has not previously been a strong predictor for semen quality. Nevertheless, the current report represents the first examination of a relationship between parental age and a son's semen quality. While the incidence of many diseases of the offspring increases with both advanced maternal and paternal age (Hook *et al.*, 1983; Lehmann and Chism, 1987; Goriely and Wilkie, 2012), the current report suggests that male sperm production is not affected by parental age.

Authors' roles

M.L.E., T.J.K. and L.P. conceived the study. All authors had a role in the design of the study. E.B., R.L.J. and L.P. obtained the data. L.P. did the data linkage, cleaning and statistical analyses. All authors interpreted the data. M.L.E. and L.P. drafted the article and all authors took part in revising it for critically important intellectual content and all gave final approval of the version to be published.

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Conflict of interest

None declared.

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