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Original Article

Reproductive epidemiology

Semen quality and lifespan: a study of 78 284 men followed for up to 50 years

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ABSTRACT

STUDY QUESTION: Is semen quality associated with the lifespan of men?

SUMMARY ANSWER: Men with a total motile sperm count of >120 million could expect to live 2.7 years longer than men with total motile sperm count of >0–5 million.

WHAT IS KNOWN ALREADY: Male infertility and semen quality have been suggested to be markers of morbidity and thus mortality, but the role of underlying disease present at time of semen quality evaluation has not been thoroughly assessed. The aim of this study was to determine the association between semen quality and mortality, and to assess the impact of the health of the man prior to semen quality assessment.

STUDY DESIGN, SIZE, DURATION: The study was based on 78 284 men who had their semen quality assessed between 1965 and 2015 at the public semen analysis laboratory in the Copenhagen area, Denmark, due to reported couple infertility. Thus, the included men covered a wide range of semen quality. Semen quality assessment included semen volume, sperm concentration, and the proportion of motile and morphologically normal sperm, from which the total sperm count and the total motile sperm count were calculated. Utilizing the unique Danish national registers, follow-up of the men regarding all-cause mortality was performed with a median follow-up of 23 years (5–95th percentile: 8–45 years) during which 8600 deaths occurred, accounting for 11.0% of the total population.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Life expectancy was calculated according to semen quality. Furthermore, the relative differences in mortality were estimated using Cox regression analyses and presented as hazard ratios (HRs) with 95% CIs. A more recent subpopulation of 59 657 men delivered semen samples between 1987 and 2015, a period in which information on educational level and diseases prior to semen sampling was available and adjusted for in Cox regression analyses.

MAIN RESULTS AND THE ROLE OF CHANCE: Men with a total motile count of >120 million could expect to live 80.3 years, compared to 77.6 years among men with total motile count of >0–5 million. In Cox regression analyses, all semen parameters were negatively associated with mortality in a dose–response manner both in the total population and the more recent subpopulation (*P*-trend for all semen parameters <0.001), and adjustment for educational levels and prior diagnoses did not change the estimates in the latter. Looking at total motile sperm count as an example, men with a total motile sperm count >120 million served as the reference, and the adjusted HRs for all-cause mortality in the more recent subpopulation were: azoospermia: 1.39, >0–5 million: 1.61, >5–10 million: 1.38, >10–40 million: 1.27, >40–80 million: 1.16, >80–120 million: 1.19, *P*-trend < 0.001.

LIMITATIONS, REASONS FOR CAUTION: The study was well-powered and included a unique database of results from semen analyses combined with register follow-up. However, we did not have information on health behaviours, and assessment of the health of men prior to semen sampling was limited to diagnoses obtained from the National Patient Register, and only applied to a subpopulation of men. A further limitation is that the group of men with azoospermia represents a heterogeneous group regarding testicular function as they could not be stratified into those having obstructive azoospermia and those having non-obstructive azoospermia.

WIDER IMPLICATIONS OF THE FINDINGS: We observed clear negative dose–response associations between all semen parameters and all-cause mortality. The associations were not explained by educational levels or diseases registered at the time of semen evaluation. Thus, some men with impaired semen quality may experience less healthy ageing than men with better semen quality and

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could benefit from being identified at the time of semen quality evaluation. However, finding relevant biomarkers to identify the subgroups of men at increased risk will be key to initiating relevant prevention strategies.

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Introduction

Male infertility is a critical clinical problem for couples facing difficulties conceiving but the public health relevance of semen quality may extend beyond fertility and reproduction. There is a growing body of evidence suggesting that male infertility and semen quality are associated with a higher lifetime incidence of certain diseases and shorter life expectancy (Murshidi *et al.*, 2020; Fallara *et al.*, 2024). One study found higher mortality in men with male factor infertility compared to men in infertile couples without a male factor (Eisenberg *et al.*, 2014), while others have reported higher mortality only in men with azoospermia and not in those with oligozoospermia (Glazer *et al.*, 2019; Del Giudice *et al.*, 2021). Semen quality has, however, been linked to mortality in a dose-dependent manner, suggesting that a concern of impaired health is not limited to only men with azoospermia. A long-term follow-up among 43 277 men without azoospermia but referred for couple infertility (a subset of the population in the present study) showed that mortality decreased with higher sperm concentrations up to a threshold of 40 million/ml, a value which is substantially higher than the current World Health Organization's lower reference limit of 16 million/ml (World Health Organization, 2021). Mortality also decreases as the percentages of motile and morphologically normal spermatozoa increase (Jensen *et al.*, 2009).

Most infertile men present without any major comorbidities at the time of their fertility assessment, as they are still relatively young. However, it is well established that on a group level, infertile men have more comorbidities at the time of fertility evaluation than comparable fertile men (Salonia *et al.*, 2009; Eisenberg *et al.*, 2015; Ventimiglia *et al.*, 2015). When studying the association between fertility and mortality among men evaluated for infertility, Eisenberg *et al.* (2014) adjusted for comorbidities at the time of fertility evaluation in a subset of the population, which attenuated the observed association. This indicates that poorer health in infertile men at the time of infertility diagnosis could partly explain the observed long-term association between semen quality and mortality. However, with a mean follow-up time of 7.7 years, this study only included 69 cases with a mean age of death of 44.1 years, and it remains to be seen what roles the diagnoses prior to semen quality assessment play in the long-term association between semen quality and mortality.

Furthermore, the majority of studies examining the association of male fertility with mortality have only evaluated indicators of male reproductive function, such as fatherhood (Eisenberg *et al.*, 2011; Elenkov *et al.*, 2020), infertility diagnosis or type of fertility treatment (Eisenberg *et al.*, 2014; Glazer *et al.*, 2019; Lundberg *et al.*, 2019; Del Giudice *et al.*, 2020), or the couple fecundity marker, time-to-pregnancy (Ahrenfeldt *et al.*, 2021; Lindahl-Jacobsen *et al.*, 2024); only a few studies have evaluated the impact of semen quality (Groos *et al.*, 2006; Jensen *et al.*, 2009). Semen quality is relevant to consider since growing evidence suggests that semen parameters are related to increased morbidity and shorter life expectancy, even at levels above the cut-off values usually used for the diagnosis of male factor infertility, thus semen quality may be a universal biomarker of morbidity and mortality, also of relevance for men with proven and untested fertility.

Thus, based on a large semen quality database with up to 50 years of register follow-up, we have investigated the association between semen quality and all-cause mortality, taking into account hospital diagnoses received during the 10 years prior to semen testing.

Materials and methods

Study population and design

This register follow-up study is based on the Danish Semen Quality Database (DaSe), which consists of men delivering a semen sample from 1963 to 2015 at the public semen analysis laboratory in the Copenhagen area, The Copenhagen General Practice Laboratory. These data have been cleansed, validated, and stored in the CopLab database (Kriegbaum *et al.*, 2024). Men had been referred to the laboratory by a general practitioner, urologist, or gynaecologist for screening of semen quality due to self-reported couple infertility and before determination of additionally needed diagnostics or treatments. Semen results, therefore, represent a broad spectrum of semen quality, from men with azoospermia to men having very good semen quality. Men were included in the current study if they delivered a semen sample from 1965 (there were only a few observations before that), if they were between 18 and 65 years old at the time of sample delivery, and if the database included information on at least their sperm concentration and period of abstinence. In total, 78 284 men with relevant data from DaSe could be identified in the Danish Civil Registration System and are included in the present study with registry data on follow-up. In addition, a subpopulation with health data available for at least 10 years before semen sample delivery included men delivering samples from 1987 onwards (N = 59 657). Details are presented in a flow chart in Supplementary Fig. S1.

Data on a subset of the population in the present study (N = 43 277), who delivered a semen sample before 2001 and where men with azoospermia were excluded, have been published previously (Jensen *et al.*, 2009). In the present study, the follow-up has been expanded considerably with the end of follow-up moving from 2001 to 2023; additionally, the men with azoospermia (N = 4829) were included after careful individual data evaluation of causes of referral and notes about the semen findings to ensure that they did not deliver semen samples for an assessment after a vasectomy procedure.

Exposure assessment (semen quality)

Reporting of semen quality assessment is conducted according to the recommended specifications (Björndahl *et al.*, 2016). Before delivery of the semen sample to the laboratory, the men had

been asked to keep an ejaculation abstinence period of 3–4 days, and the actual abstinence period was recorded. The semen samples were produced at the laboratory or at home with instructions to bring the sample to the laboratory protected from extreme temperatures within 1 h after ejaculation. The laboratory used standardized analysis methods throughout the collection period. From 1980, the methods relied on the World Health Organization guidelines (World Health Organization, 1980), which were in accordance with the methods used up to this time point. Briefly, all specimens were analysed within 1 h of ejaculation into a standard tube. Immediately after receipt and no 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 (Bostofte *et al.*, 1982a,b; Jensen *et al.*, 2009). Until 2012, morphology was assessed according to the original WHO criteria (World Health Organization, 1980) and, after that, according to strict criteria (Menkveld *et al.*, 1990; World Health Organization, 1999). Total sperm count was calculated by multiplying semen volume and sperm concentration, and the total motile sperm count was calculated as total sperm count multiplied by the proportion of motile sperm.

Some men delivered several semen samples, but only the first sample from each man is included in the present study. For statistical analyses, all semen parameters were categorized (see Fig. 1 for the specific categorizations). To allow for morphology results, assessed with different criteria, to be analysed together, men were divided into six groups based on percentiles (<5, 5–25, 25–50, 50–75, 75–95, or >95 percentile) of their sperm morphology, calculated separately for the two assessment criteria, after which the similar categories were combined.

Outcome assessment (all-cause mortality)

Information from the first semen sample (considered baseline) from each man was included and linked to Danish registers using the personal identification number, which was first given to all Danish citizens alive in 1968 and to all newborns and immigrants after that (Pedersen, 2011). This allowed us to have accurate and efficient individual data linkage between the DaSe and the registers used in the present study. The Centralized Civil Register provided follow-up information on vital status and date of death or emigration from 1965 until the end of follow-up, 31 December 2023.

Covariate assessment

The period of abstinence before sample delivery was recorded, and the variable was categorized for statistical analyses (≤1, 1–≤2, 2–≤3, 3–≤4, 4–≤5, 5–≤6, and >6 days). The period (year) of sample delivery was categorized into 5-year groups, and the age at sample delivery was calculated.

Educational level was available from the Population Education register from 1980 (Statistics Denmark, 2024). The highest level of education that each man had completed at the time of sample delivery was obtained. If no information was available in the baseline year, the earliest information from the following years was used. According to the International Standard of Education (ISCED), the educational level was grouped into low (ISCED levels 0–2), medium (ISCED levels 3–4), and high (ISCED level 5+) educational levels.

The National Patient Register (Schmidt *et al.*, 2015) contains all contacts to somatic hospital departments since 1977 and was used to identify diagnoses prior to semen quality assessment. Diagnoses are registered by WHO International Classification of Diseases (ICD) codes, with the eighth revision (ICD-8) used before 1994 and subsequently the 10th revision (ICD-10) was used. We retrieved information on all diagnoses received within the 10 years prior to semen sample delivery. Diagnoses were grouped via a grouping of 99 diagnoses, further combined into 15 relevant main groups as defined by Statistics Denmark (2023). For the statistical analyses, dummy variables were constructed for these main groups.

Statistical analyses

Basic description

Basic characteristics and semen parameters were described with medians and 5–95 percentiles or frequencies for the total study population and stratified by period of sample delivery (before 1987 or from 1987 and onwards). Similarly, educational level and prior diagnoses were described for the subpopulation delivering a semen sample 1987–2015.

Restricted mean survival time

Using the non-parametric restricted mean survival time (RMST) analysis, absolute measures of life expectancy until age 90 years and according to semen quality were illustrated for each semen parameter category. The mean survival time calculations were conditioned on having survived until the age of sample delivery.

Cox regression analyses

The longitudinal associations between categorized semen parameters and all-cause mortality were analysed using Cox regression to estimate the hazard ratios (HRs) and 95% CIs. All men were followed from the age at delivery of their first semen sample until age at death, emigration, or end of follow-up, whichever came first. In the basic Model 1, used to analyse data from the total population and repeated for the subpopulation, age was used as the underlying time scale and strata of the period of sample delivery in 5-year intervals were included to account for calendar effects (Canchola *et al.*, 2003), with further adjustment for the period of abstinence. The main Model 2, used to analyse data for men delivering a semen sample between 1987 and 2015, was constructed as described above with further adjustment for educational level as a proxy for socioeconomic status and the health status of the men defined by all diagnoses registered in the National Patient Register in the 10 years before semen quality assessment (included as dummy variables as previously described). The proportional hazards assumption was checked visually by plotting the Schoenfeld residuals according to time (Grambsch and Therneau, 1994).

Sensitivity analyses

(i) To assess the robustness of adjustments and any modifying effect of health, analyses were repeated in the two strata consisting of men with and without any registered diagnoses in the 10 years prior to baseline, respectively. (ii) To elucidate the influence of potential undiagnosed diseases before and at baseline, which could affect both semen quality and mortality risk, the main Model 2 was repeated after introducing a 5-year immortality period from baseline (thus only deaths occurring more than 5 years after baseline were included). (iii) To examine how follow-up time influenced the results, analyses in Model 1 were repeated for total motile sperm count, stratified by 10-year periods of study entry. The number of men delivering samples between 1965 and 1975 was limited, and therefore this period was combined with the following. (iv) Finally, morphology analyses, in which categorization was based on percentiles due to a shift in assessment method, were repeated after excluding counts based on strict criteria.

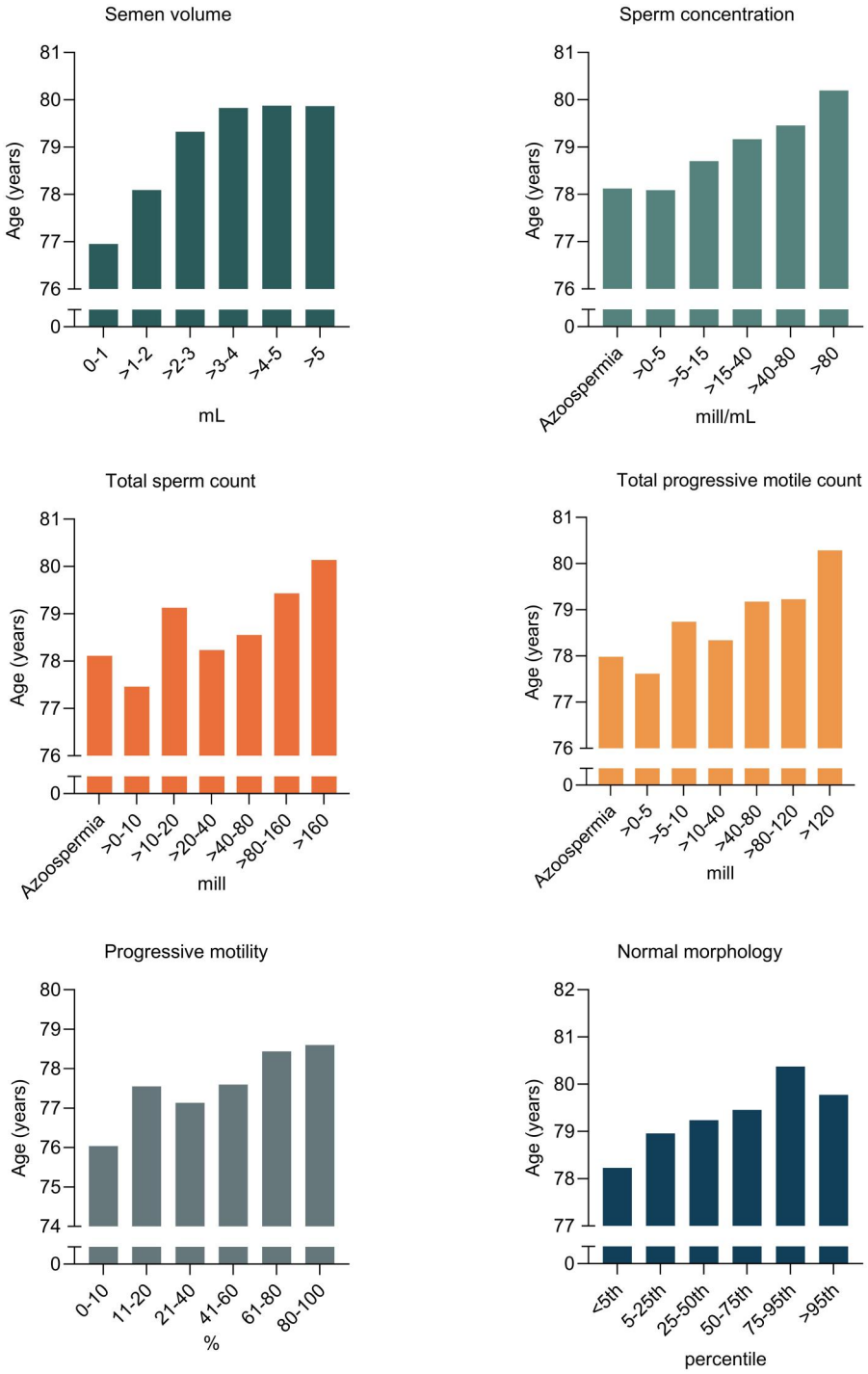

Figure 1. Expected age of death (restricted mean survival time) according to semen quality, based on the total population of 78 284 men. Bars represent the mean expected age of death within each category.

Statistical analyses were conducted in SAS (version 9.4 M8), the statistical software package SAS Institute (SAS Institute Inc, Cary, NC, USA).

Ethical approval

The study was approved by the Danish Data Protection Agency and registered in the data processing inventory of the University of Copenhagen (J. no. 514-0460/20-3000). Danish law does not require informed consent for registry studies using administrative data. All information was anonymized prior to statistical analysis.

Results

Basic description

The total study population consisted of 78 284 men, of whom 8600 (11.0%) died during follow-up (median follow-up time: 23 years). The men had a median age of 32 years at time of delivery of the semen sample (Table 1). Median sperm concentration was 46 million/ml (5–95 percentile: 0–182 million/ml). See Table 2

Table 1. Basic description of study population (total and subpopulations with sample delivery 1965–1986 and 1987–2015, respectively).

	Total population (N = 78 284)	Sample delivery 1965–1986 (N = 18 627)	Sample delivery 1987–2015 (N = 59 657)
Age, years	32 (24–44)	30 (23–42)	32 (24–44)
Birth year	1964 (1944–1982)	1949 (1937–1959)	1969 (1952–1983)
Sample year	1997 (1977–2014)	1980 (1975–1986)	2002 (1988–2014)
Follow-up time, years	23 (8–45)	40 (9–47)	20 (8–35)
Deaths, % (n)	11.0 (8600)	29.8 (5541)	5.1 (3059)

Data are illustrated as median (5–95 percentile) or frequency (N).

for a description of other semen parameters. The subpopulation of men delivering a semen sample from 1987 to 2015 also had a median age of 32 years at baseline and was followed for a median of 20 years with 3059 (5.1%) deaths occurring (Table 1). Semen parameters in this subpopulation were similar to those of the entire population, although sperm concentration and total sperm count were slightly higher (Table 2). In the subpopulation, 20.7% had received a diagnosis (any) in a hospital setting in the 10 years before baseline, most frequently related to fractures and ill-defined conditions (10.4% and 6.1%, respectively), while only a few had another diagnosis, e.g. malignancies (0.6%) or nutritional and metabolic related diagnoses (0.4%). See Table 3 for the frequency of diagnoses in all disease groups. Men with a prior diagnosis tended to have a higher sperm concentration than those without (median: 51 vs 47 million/ml). Still, the sperm concentration was lower for the specific subgroups of men with prior malignancies (median: 35 million/ml), diseases related to the circulatory system (median: 44 million/ml) or the genitourinary system (median: 43 million/ml) compared to those without these diagnoses (median: 48 million/ml).

Semen quality and restricted mean survival time

In absolute terms, men with azoospermia or a total motile count >0–5 million had a life expectancy of 78.0 and 77.6 years, respectively, while it was 80.3 years for men with a total motile count >120 million, corresponding to a reduction in life expectancy of 2.3 and 2.7 years ($P < 0.001$). Similar differences between the lowest and highest semen quality categories were observed for the other semen parameters (Fig. 1).

Semen quality and all-cause mortality

For the total population (N = 78 284), all semen parameters were negatively associated with all-cause mortality in a dose–response manner (P-trend <0.001 for all semen parameters). However, the higher mortality risk for men with azoospermia tended to be slightly less pronounced than for the next category of men (with sperm concentration >0–5 million/ml, total sperm count >0–10 million or total motile sperm count >0–5 million). Men with azoospermia had an HR = 1.28 (95% CI: 1.12; 1.46), while men with a total motile sperm count of >0–5 million had an HR = 1.46 (95% CI: 1.35; 1.59) compared to the reference of men with a total motile count >120 million (Fig. 2A and Supplementary Table S1).

Results based on the subpopulation delivering a semen sample from 1987 to 2015 (N = 59 657) showed similar trends as for the total population, but the estimates were more pronounced (Supplementary Table S1). For example, in this sample, men with azoospermia had an HR = 1.52 (95% CI: 1.15; 2.02), while men with a total motile sperm count of >0–5 million had an HR = 1.70 (95% CI: 1.50; 1.93) compared to the reference. After adjustment for educational status and diagnoses before baseline, the observed differences in survival persisted (P-trend <0.001 for all semen parameters), but most HRs were slightly attenuated. In the adjusted analyses, compared to the reference with a total motile count >120 million, all other groups had significantly higher mortality risk with no apparent threshold (azoospermia: HR = 1.39 (95% CI: 1.05; 1.85), >0–5 million: HR = 1.61 (95% CI: 1.42; 1.83), >5–10 million: HR = 1.38 (95% CI: 1.14; 1.68), >10–40 million: HR = 1.27 (95% CI: 1.13; 1.42), >40–80 million: HR = 1.16 (95% CI: 1.03; 1.29), and >80–120 million: HR = 1.19 (95% CI: 1.06; 1.34)) (Fig. 2B and Supplementary Table S1).

Sensitivity analyses

When stratifying analyses on men with and without any prior diagnoses, results based on men without prior diagnoses were very similar to the adjusted results. The group of men with prior diagnoses was limited in size, and thus, CIs for the estimates were wider. However, the overall impression was that associations between semen quality parameters and all-cause mortality were more pronounced in men with prior diagnoses (Supplementary Table S2).

When limiting events to deaths occurring more than 5 years after baseline, the overall results did not change, and HRs were of similar magnitude as in the main Model 2 (data not shown).

Repeated analyses, stratified by period of sample delivery to explore the role of length of follow-up, revealed no clear pattern (data not shown).

Results for morphology excluding counts assessed with strict criteria were comparable to those from the main analysis (data not shown).

Discussion

In this large study combining semen quality and register data, following men for up to 50 years, we observed that lower semen quality was associated with increased all-cause mortality in a dose–response manner for all semen parameters. In absolute numbers, men with a total motile count >120 million had a 2.7-year longer life expectancy than men with a total motile count >0–5 million. The association between semen quality and mortality was not explained by diseases present at the time of semen sampling, which could affect both semen quality and long-term survival. Our study, measuring semen quality rather than crude categorizations such as fatherhood or infertility diagnosis, clearly demonstrated that semen quality parameters as a marker for long-term survival are relevant even at semen quality levels much higher than the cut-off values usually used for diagnosis of male factor infertility.

Results from our prior study (Jensen *et al.*, 2009) and this study, expanding the study population and follow-up time of our previous study considerably and including health information prior to semen sampling, are consistent overall. Our results also align with prior studies finding that male reproductive function is a biomarker of long-term survival (Groos *et al.*, 2006; Jensen *et al.*, 2009; Eisenberg *et al.*, 2014; Glazer *et al.*, 2019;

Table 2. Semen quality of study population (total and subpopulations with sample delivery 1965–1986 and 1987–2015, respectively).

	Total population (N = 78 284)		Sample delivery 1965–1986 (N = 18 627)		Sample delivery 1987–2015 (N = 59 657)	
	N	Median (5–95 percentile)	N	Median (5–95 percentile)	N	Median (5–95 percentile)
Period of abstinence, days	78 284	3.5 (2.0–5.0)	18 627	3.5 (2.0–4.5)	59 657	3.5 (2.0–5.5)
Semen volume, ml	78 190	3.2 (1.2–6.2)	18 602	3.2 (1.1–6.3)	59 588	3.2 (1.4–6.2)
Sperm concentration, million/ml	78 284	46 (0–182)	18 627	37 (0–163)	59 657	48 (0.2–188)
Total sperm count, million	78 190	144 (0–566)	18 602	113 (0–508)	59 588	154 (0.5–580)
Motile sperm, %[a]	73 393	68 (30–81)	15 841	66 (17–82)	57 552	68 (33–81)
Total motile count, million[a]	73 310	105 (1–414)	15 819	95 (0.3–389)	57 491	108 (2–420)
Morphology until 2011, %[a,b]	64 308	63 (25–85)	14 861	66 (28–84)	49 447	61 (24–86)
Morphology, strict criteria, %[a,b]	7574	4 (1–11)	0	–	7574	4 (1–11)

Data are illustrated as median (5–95 percentile).
[a] Men with azoospermia are not included, explaining the lower numbers.
[b] From 2012, morphology was assessed using strict criteria (WHO 2010).

Table 3. Educational status and registered hospital diagnoses of the subpopulation with sample delivery 1987–2015.

	Sample delivery 1987–2015 (N = 59 657)
Education, % (n)	
Low	16.4 (9752)
Medium	41.3 (24 616)
High	40.2 (23 960)
Unknown	2.2 (1329)
Any diagnosis before baseline, % (n)[a]	20.7 (12 331)
Infections	0.8 (473)
Malignancies	0.6 (345)
Nutritional and metabolic	0.4 (213)
Blood and blood forming organs	0.1 (55)
Mental disorders	0.2 (89)
Nervous system and sensory organs	1.3 (765)
Circulatory system	0.7 (421)
Respiratory organs	1.2 (702)
Digestive system	1.4 (856)
Genitourinary system	1.0 (615)
Skin and subcutaneous tissue	0.9 (517)
Musculoskeletal and connective tissue	2.8 (1643)
Congenital malformations	0.2 (133)
Ill-defined	6.1 (3618)
Fractures etc.	10.4 (6182)

Data are illustrated as frequency (N).
[a] Any registered diagnosis within the 10 years prior to baseline. Men can have more than one diagnosis. Thus, the sum of specific diagnoses exceeds the number of men with any diagnosis before baseline.

Del Giudice *et al.*, 2020; Elenkov *et al.*, 2020; Ahrenfeldt *et al.*, 2021). In contrast, a large register-based Swedish study observed no overall increased mortality risk among infertile men compared to men without such a diagnosis (Lundberg *et al.*, 2019), but in general, couples who are diagnosed as infertile are a selected population with lower mortality than the general population and thus, external comparisons can be difficult. Our previous study also reported lower mortality in the total population of men delivering a semen sample at the public semen analysis laboratory in the Copenhagen area than in the age-standardized general population of Danish men. However, within the studied population, an association between semen quality and mortality was still observed (Jensen *et al.*, 2009).

To our knowledge, our results are the first to describe the association between semen quality and life expectancy, in contrast to our previous publication, which only reported relative differences in mortality risk (Jensen *et al.*, 2009). Thus, there are no other publications available for a direct comparison, but one study reported that men with a sperm concentration of 0–5 million/ml were, on average, hospitalized 7 years earlier than men with a sperm concentration of 195–200 million/ml (Latif *et al.*, 2017), underlining that men with impaired semen quality as a group not only can expect to die earlier but also to live fewer healthy years.

Del Giudice *et al.* (2021) reported that the observed association between oligozoospermia and mortality remained after excluding prevalent cardiovascular and malignant disease (i.e. within 1 year of the index date determining categorization as infertile or not). Similarly, in our study, the associations remained and were only slightly attenuated after considering the educational status and any hospital diagnoses received within the 10 years before semen quality testing, and even in sensitivity analyses excluding deaths within 5 years after baseline, supporting that the association is not due to reverse causality (already identified poor health causing impaired semen quality). However, the association may be due to unrecognized poorer health or a common risk factor for poor health and reproductive function. Thus, the fertility work-up may be a window of opportunity for preventive initiatives if we can identify the subgroup of men at increased risk of impaired health in the future. Men with severely impaired semen quality due to current or prior disease (or its treatment) are likely rather sick and at increased risk of dying *per se*, and this may explain the results of our sensitivity analysis indicating that the excess mortality in men with impaired semen quality was even larger in men with registered diagnoses before semen analysis than in men without prior diagnoses. Thus, the major preventive potential may lie in the group of men without such prior diseases. We have previously shown that in young Danish men (median age 19 years), who are considered healthy, semen quality and reproductive hormones were associated with minor differences in cardiometabolic health markers (Hansen *et al.*, 2023). Similarly, Hart *et al.* (2019) reported that a significant minority of 20-year-old Australian men presented with features of metabolic syndrome, and that adverse cardiometabolic features were associated with impaired testicular function. Whether these differences will develop into overt health differences is yet unknown.

Strengths and limitations

The study has several strengths. It is based on, by far, the largest semen quality database available, which can be linked with health information from valid registers and with an extended follow-up of up to 50 years for the earliest included men with almost no loss-to-follow-up. In contrast to other proxies of male

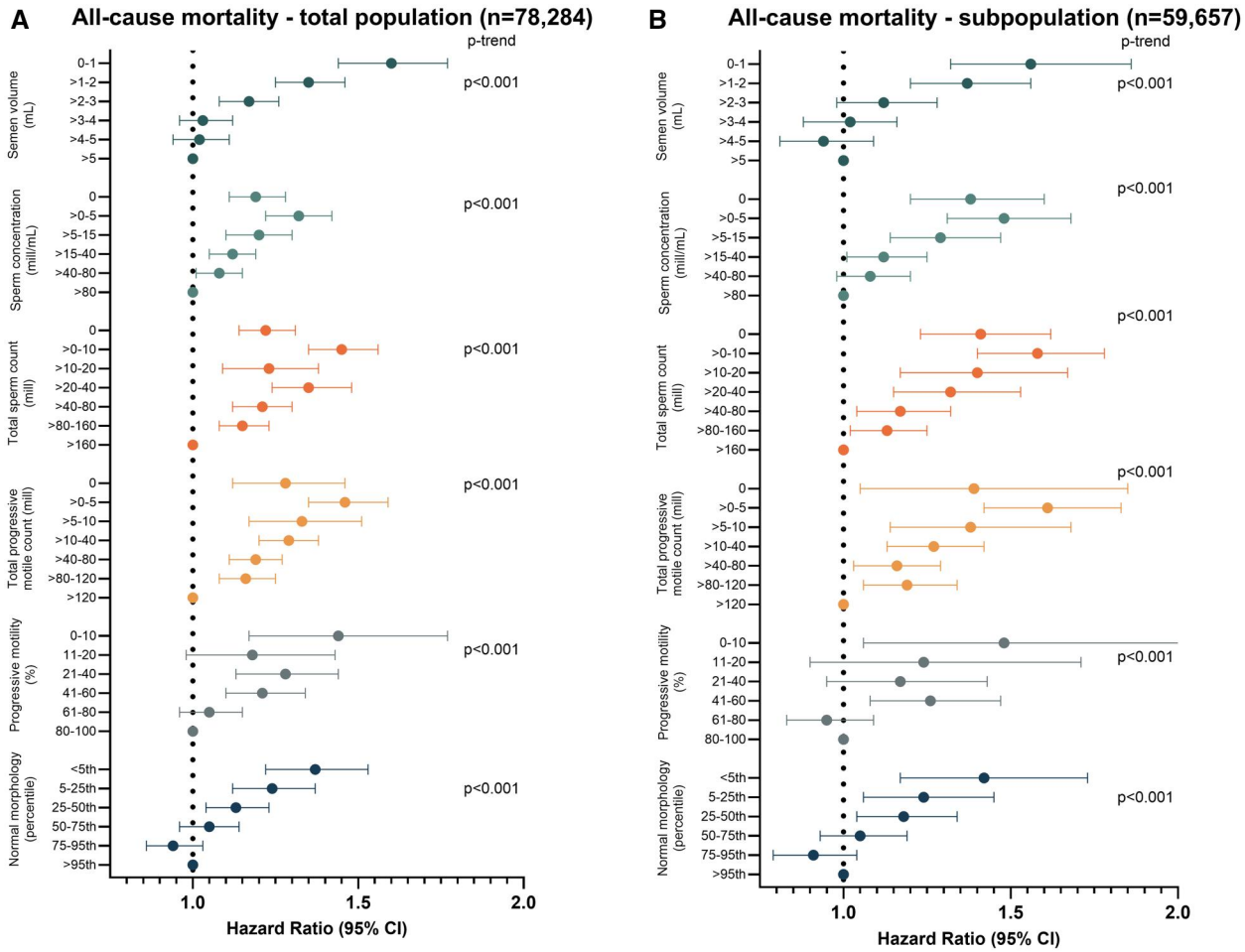

Figure 2. All-cause mortality according to semen quality. Analyses are based on (**A**) the total population of 78 284 men studied from 1965 to 2015 and (**B**) the more recent subpopulation of 59 657 men studied from 1987 to 2015. Data are presented as adjusted hazard ratios with 95% CIs. Results are from Cox regression analyses. Results in panel (A) are based on the basic Model 1, with attained age as the underlying time scale, including strata of period of semen sampling (5-year intervals), and adjusted for period of abstinence. Results in panel (B) are based on the main Model 2, constructed as described above with further adjustment for educational status and any diagnoses prior to baseline.

reproductive function, such as fertility treatment and fatherhood, semen quality is not affected by fertility intentions, which might be a significant confounding factor in other studies, complicating the process of selecting a relevant comparison group in contrast to the present study which relied on internal comparisons. It is well known that the population seeking fertility treatment is healthier than the background population, which may hamper the generalizations of the observed associations.

Although the included men are well-described based on register data, a limitation is that information exceeding what can be obtained from the registers is lacking, e.g. information on health behaviours which could confound the studied associations. However, educational level was included as a crude proxy for socioeconomic status and thus health behaviour, and adjustment did not change the associations. In addition, a prior study has shown that smoking, BMI and educational level do not modify the association between semen quality and hospitalizations (Latif *et al.*, 2018). Unfortunately, information regarding fatherhood status of the included men was not available either but, in our previous study, this did not explain the observed association between semen quality and mortality (Jensen *et al.*, 2009). Furthermore, assessment of the health of men prior to semen sampling was based on diagnoses registered in the National Patient Register, and presence of diagnoses from the general practitioner or undiagnosed health issues cannot be ruled out. Lastly, no genetic data, data on reproductive hormone levels, or biobank material were available, which could be used to elaborate on mechanisms behind observed associations.

We did not observe the highest mortality risk in the group of men with azoospermia as has been reported in other studies (Glazer *et al.*, 2019; Del Giudice *et al.*, 2021) but rather among men with very few spermatozoa in their sample (below 5 million/ml). Although we excluded men who delivered semen samples for assessment after a vasectomy procedure, it cannot completely be excluded that some of these had been misclassified as fertility patients. However, a more likely explanation is that the group of men with azoospermia consists of two subgroups, i.e. men with obstructive azoospermia and basically well-functioning spermatogenesis as well as men with non-obstructive azoospermia with severely impaired or completely ceased spermatogenesis. The first subgroup would attenuate the association between azoospermia and mortality.

Conclusion

In conclusion, semen quality was found to be a strong marker of mortality. Men with very good semen quality could expect to live, on average, more than 2 years longer than men with severely impaired semen quality. The dose–response association between semen quality and mortality was observed for all included semen parameters, and diagnosed diseases or educational levels at the

time of semen quality assessment did not explain the associations. Before preventive initiatives can be initiated, further studies are needed to identify late-occurring morbidities associated with semen quality. Thus, future studies should focus on disease trajectories according to semen quality as well as early biomarkers that could be relevant disease markers in infertile men.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Data availability

The data underlying this article cannot be shared publicly due to data protection rules. The data will be shared on reasonable request to the corresponding author after relevant permissions have been obtained.

Authors' roles

Substantial contribution to conception and design: all authors. Data acquisition: L.P., R.L.-J., M.K., B.S.L., V.S., C.L.A., and N.J. Data analysis: L.P., R.L.-J., and N.J. Data interpretation: all authors. Drafting the article: L.P. and N.J. Critical revision of the article for important intellectual content: all authors. All authors have approved the final version of article and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare no conflicts of interest.

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