

Original Contribution

Good Semen Quality and Life Expectancy: A Cohort Study of 43,277 Men

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Fertility status may predict later mortality, but no studies have examined the effect of semen quality on subsequent mortality. Men referred to the Copenhagen Sperm Analysis Laboratory by general practitioners and urologists from 1963 to 2001 were, through a unique personal identification number, linked to the Danish central registers that hold information on all cases of cancer, causes of death, and number of children in the Danish population. The men were followed until December 31, 2001, death, or censoring, whichever occurred first, and the total mortality and cause-specific mortality of the cohort were compared with those of all age-standardized Danish men or according to semen characteristics. Among 43,277 men without azospermia referred for infertility problems, mortality decreased as the sperm concentration increased up to a threshold of 40 million/mL. As the percentages of motile and morphologically normal spermatozoa and semen volume increased, mortality decreased in a dose-response manner ($P_{\text{trend}} < 0.05$). The decrease in mortality among men with good semen quality was due to a decrease in a wide range of diseases and was found among men both with and without children; therefore, the decrease in mortality could not be attributed solely to lifestyle and/or social factors. Semen quality may therefore be a fundamental biomarker of overall male health.

cohort studies; fertility; life expectancy; mortality; semen analysis

Several epidemiologic studies indicate that male reproductive disorders have become more prevalent during the last 50 years. The incidence of testicular cancer has increased (1) and, at the same time, sperm counts appear to have declined (2, 3), although geographic variations tend to blur the picture. In both cases, the increased incidence seems to follow a birth cohort pattern (4, 5). The incidences of congenital malformation of the male reproductive tract (6, 7) may also have increased. Testicular cancer is associated with maldescent of the testis (8), reduced semen quality, and decreased fertility before the cancer is diagnosed (9, 10). Against this background, it has been proposed that these conditions are all symptoms of one underlying entity, the testicular dysgenesis syndrome, with a common origin in fetal life (11). The fetal environment has also been suggested to influence later health (the “fetal origins hypothesis” (12)), as fetal malnutrition in utero and early life increases the risk of common adult diseases, such as cardiovascular disease and diabetes. The mechanisms by which the early life conditions are associated with male reproductive disorders and major late-life diseases are still not well

understood, and it is unclear whether there is overlap in the mechanisms. If the intrauterine factors that affect late-life major disease occurrence also influence the male reproductive system, it can be expected that semen quality is associated with both male disease occurrence and mortality.

Semen quality is known to be a marker of fertility, and a sperm concentration of up to 40 million/mL has been found to increase the probability of conception in a menstrual cycle (13). Fertile couples are known to survive longer, but it is not determined whether this is due to biologic and/or social factors (14–17). The association between semen quality and long-term health effects has, to our knowledge, not been studied. A study (presented at the Third European Congress of Andrology) of 854 men of whom 192 were deceased found that men with normal semen quality survived longer (20% deceased) than men with poor semen quality (29% deceased) (18). The study, however, did not take the age of participants and length of follow-up into account.

Studying the association between semen quality and subsequent mortality demands a large sample size and long

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periods of follow-up. In addition, it is important to allow for confounding factors, most importantly fertility status, which is clearly associated with both semen quality and mortality. The Copenhagen Sperm Analysis Laboratory has examined semen samples from more than 50,000 men from 1963 to 2001, and the Danish Civil Registration System makes it possible to obtain information on mortality and fertility status. In this unique data set, we therefore studied the associations between semen characteristics and subsequent mortality from different causes, taking into account fertility status testing the hypothesis that semen quality predicts subsequent mortality from all causes.

MATERIALS AND METHODS

One of several public semen analysis laboratories in Denmark, the Copenhagen Sperm Analysis Laboratory examines semen samples from men mostly living in the Copenhagen area. Men are referred to the clinic by general practitioners and urologists, and the investigations are publicly funded. No sperm banking is provided at the laboratory. The men are classified according to the following diagnoses by physicians in the laboratory: vasectomy, infertility, azospermia, and other. It was generally accepted that the period of infertility before referral had to be 2 years. If the first delivered semen sample was not normal, the man was contacted and asked to deliver a second sample shortly after the first. In addition, some men delivered more than one semen sample after longer time periods. A total of 38% of the men delivered more than one sample, and 67% did so within a few months of the first sample. Therefore, in this study, we included only the first semen sample in the analysis. The methods used for analysis of semen have been described previously (19–22). The sperm concentration (million/mL), penetration length (mm), and percentages of immotile and morphologically abnormal spermatozoa were calculated according to the World Health Organization classification of subfertility (23). The semen analysis procedures have remained unchanged during the study period, and one of the technicians has worked in the laboratory for more than 40 years. The period of abstinence before the delivery of the semen sample was also recorded.

All men referred to the Copenhagen Sperm Analysis Laboratory for evaluation of their semen quality from 1963 to 2001 were included. Through their unique personal identification numbers held by all Danish people, the men were linked to the Danish Cancer Registry, the National Death Register, and Statistics Denmark, which hold information on all cases of cancer, causes of death, and number of children (including adopted children), respectively, in the Danish population. The men were followed from the date of first semen analysis until December 31, 2001, death, or censoring, whichever occurred first.

Mortality rates were calculated according to referral diagnosis and first compared with the total mortality rates of the Danish male population. Data on deaths and the midyear population for all Danish men were retrieved from Statistics Denmark's digital database (www.statistikbanken.dk). All mortality rates were stratified by 1-year age groups

and 1-year calendar groups. Mortality rates were analyzed as a function of the covariates by using multiplicative Poisson regression models (24), and standardized mortality ratios and 95% confidence intervals were thereby estimated. The analyses were stratified according to later occurrence of testicular cancer, which occurred among 43 men, which did not affect the results, and therefore these men were not excluded.

Men referred for infertility without azospermia were selected for further analysis. Total mortality rates were compared for men according to semen characteristics (categorized) within the study population of infertile men without azospermia. The analyses were then repeated after stratification on total number of children. Then, specific cause mortality (categorized into 9 major groups) was compared among men with a sperm concentration <20 and ≥ 20 million/mL. All analyses were conducted with the SAS, version 9.2, software package (SAS Institute, Inc., Cary, North Carolina).

RESULTS

A total of 51,543 men had a semen sample analyzed in the laboratory between 1963 and 2001. Of these, 3,556 were referred as the result of vasectomy, 43,277 for infertility problems, 4,425 with azospermia, and 285 with other diseases (parotitis, varicocele, sexual transmitted diseases, missing testicle, and testicular cancer) (Table 1). During the study period, 1,475 deaths occurred, 445 of which were from testicular cancer. The men delivering a semen sample at the Copenhagen Sperm Analysis Laboratory had a lower mortality than did the age-standardized general population of Danish men (Table 1), which is in agreement with the description of the population's being of higher social class than the general population (25). Men with vasectomies and men with azospermia had a lower mortality than did infertile men, and men with other diseases (including testicular cancer) had increased mortality (Table 1). The analyses were repeated, excluding men with testicular cancer; this did not change the findings (Table 1). These men were therefore maintained in the data material in the following analyses.

The group of men referred for azospermia was heterogeneous and comprised a number of men referred for control after vasectomy. This group has therefore in a previous publication been excluded (10, 26). Thus, in the following analyses, the study population was reduced to 43,277 men who were the male part of an infertile couple, without azospermia, and visiting the Copenhagen Sperm Analysis Laboratory between 1963 and 2001. The mortality ratios among men with different sperm characteristics are seen in Table 2. Mortality decreased as the sperm concentration increased up to a threshold of 40 million/mL, after which no further decrease in mortality was found. Mortality decreased as the percentages of motile and morphologically normal spermatozoa increased in a dose-response manner ($P_{\text{trend}} < 0.05$), whereas no effect on mortality was found with changes in semen volume and the period of abstinence (Table 2).

We then calculated the standardized mortality ratio for different causes of death among men, using men with a sperm concentration of <20 million/mL as reference. No specific causes of death contributed significantly to the

Table 1. Age- and Period-adjusted Standardized Mortality Ratios and 95% Confidence Intervals by Referral Diagnosis Among 51,543 Danish Men Visiting the Copenhagen Sperm Analysis Laboratory Between 1963 and 2001 Compared With All Age-standardized Danish Men (Reference Group)^a

Characteristics of Patients	All Men				Excluding Men Who Developed Testicular Cancer After Semen Sample Delivery			
	No. of Men	No. of Deaths	Standardized Mortality Ratio	95% Confidence Interval	No. of Men	No. of Deaths	Standardized Mortality Ratio	95% Confidence Interval
Vasectomy	3,556	63	0.55	0.41, 0.73	3,544	63	0.55	0.41, 0.74
Other ^b	285	22	0.75	0.70, 0.79	243	15	0.74	0.70, 0.79
Azospemia	4,425	268	0.42	0.19, 0.94	4,347	262	0.42	0.19, 0.95
Infertility	43,277	1,122	1.03	0.67, 1.56	42,964	1,109	0.86	0.52, 1.43

^a The analysis was repeated excluding men who developed testicular cancer after delivery of the semen sample.

^b Parotitis, varicocele, sexually transmitted diseases, missing testicle, and testicular cancer.

decreased standardized mortality ratio among men with a high sperm concentration (apart from infectious diseases), although the numbers in the different subgroups were small, and none of the differences reached statistical significance (Table 3). The group of other causes of death consisted of a variety of causes, of which ill-defined and other external causes were the largest groups followed by leukemia, mental diseases, and diabetes. Interestingly, men with a high sperm concentration did not have decreased mortality from cancers, respiratory and cardiovascular diseases, cirrhosis, or suicide (Table 3).

The men were then stratified according to fertility status (children before or after delivery of the semen sample). Childless men had increased mortality compared with fertile men (standardized mortality ratio = 1.89, 95% confidence interval: 1.67, 2.14). However, with stratification on fertility status, the same trends of decreasing mortality with increasing sperm concentrations up to 40 million/mL and with increasing percentages of morphologically normal and motile spermatozoa among fertile and childless men were found (Figure 1). The analyses were repeated among men who had children before or after the visit, and similar trends of decreased mortality with increasing semen quality were found (data not shown).

DISCUSSION

In this cohort study of more than 40,000 Danish men referred for infertility and followed for up to 40 years, a dose-response relation between good semen quality and subsequent decreased mortality was found; mortality decreased as the percentages of normal and motile sperm increased. Mortality also decreased as the sperm concentration increased up to a threshold of 40 million/mL, which mirrors the finding for the ability to conceive (13). Fertile men had a reduced mortality compared with men without children, but with stratification on fertility status, similar dose-response relations between semen quality and mortality were found among men with and without children. Interestingly, the increased mortality was due to a wide range of diseases and not particularly diseases related to lifestyle or socioeconomic status or the causes predicted by the fetal origins hypothesis (cardiovascular disease and diabetes). We therefore hypothesize that good semen quality may be

a biomarker of general health associated with better survival.

Several studies have found that a low testosterone level is associated with risk factors for cardiovascular disease (metabolic syndrome, diabetes mellitus, obesity, and hypertension) (27–30). Some longitudinal studies among older men found no association between testosterone levels and all-cause and cardiovascular mortality (31, 32). However, recent findings from a prospective study indicated increased mortality among healthy male veterans with low serum testosterone levels (33). Interestingly, high testosterone levels have been found to be related to good semen quality, but, to our knowledge, only one study has investigated the effects of poor semen quality on subsequent mortality, and this study suffered from serious methodological problems and was not age adjusted (18).

Fertile men had a lower mortality level compared with childless men, which is in line with previously published papers. This may be due to both causal mechanisms (e.g., fertile men are more likely to have a healthy lifestyle) and selection (childless men are more likely to have poor health, chronic diseases, and low socioeconomic status) (34). Some studies have suggested a relation between late age at childbearing and longer life expectancy (14, 15, 35, 36), which is also explained by both social and biologic mechanisms. Social explanations may be that higher educated couples tend to postpone childbearing and that socially marginalized women more often have children very early. For women, the ability to give birth at high ages has been interpreted as an indicator of slow aging (36), although the data are again very limited.

We found decreased mortality with increasing semen quality among both fertile and childless men, suggesting that the decreased mortality among men with good semen quality could not be attributed solely to social factors. Fertility may not be an accurate marker of the biologic ability to conceive, as some men may be childless by choice and not because of infertility problems and are thereby misclassified. Semen quality is therefore a better marker for the reproductive potential than fertility status, as we found decreased mortality among men with good semen quality and even among men with proven fertility.

This study has several advantages. It is large and has a long follow-up period and no loss to follow-up as all

Table 2. Age- and Period-adjusted Standardized Mortality Ratios and 95% Confidence Intervals in Relation to Semen Characteristics Among 43,277 Danish Infertile Men Without Azospermia Referred to the Copenhagen Sperm Analysis Laboratory for Infertility Between 1963 and 2001

Characteristics of Semen	No. of Men	No. of Deaths	Standardized Mortality Ratio	95% Confidence Interval
Sperm concentration, million/mL				
0.01–9.99	6,677	236	Reference group	
10–19.99	4,013	109	0.79	0.63, 0.99
20–39.99	7,630	170	0.60	0.49, 0.73
40–79.99	11,765	281	0.64	0.54, 0.76
≥80	13,192	326	0.66	0.56, 0.79
P_{trend}			0.57	
Semen volume, mL				
0–1.99	6,170	303	Reference group	
2–3.99	24,025	572	0.70	0.61, 0.80
≥4	13,082	247	0.57	0.48, 0.67
P_{trend}			0.14	
Percent spermatozoa with normal morphology				
0–24.99	2,497	127	Reference group	
25–49.99	3,759	160	0.72	0.59, 0.89
50–74.99	22,508	567	0.57	0.48, 0.69
≥75	14,513	268	0.46	0.37, 0.56
P_{trend}			0.02	
Percent motile spermatozoa				
0–24.99	2,357	160	Reference group	
25–49.99	5,764	199	0.75	0.60, 0.95
50–74.99	21,517	523	0.55	0.46, 0.67
≥75	13,639	240	0.52	0.42, 0.64
P_{trend}			0.04	
Penetration length, mm				
0–19.99	4,887	145	Reference group	
20–39.99	13,117	259	0.74	0.60, 0.90
40–59.99	18,412	351	0.58	0.47, 0.70
≥60	6,861	367	0.92	0.76, 1.12
P_{trend}			0.67	
Period of abstinence, days				
0–2.99	15,663	402	Reference group	
≥3	27,614	720	0.97	0.86, 1.09

participants could be traced in the Danish population registries. Both the Danish Cancer Registry and the Causes of Deaths Registry are known to be complete. In addition, the Cancer Registry is validated whereas, in the Causes of Deaths Registry, some misclassification may have occurred. This is, however, not likely to be related to semen quality, and therefore this misclassification would result in a bias toward the null hypothesis. In addition, technicians in the laboratory used the same method of analysis during the entire study period, reducing variation in semen analyses. Period of abstinence is known to affect semen quality (37) and was obtained from approximately 50% of the men. This

was not associated with subsequent mortality, and differences in the period of abstinence between men with good and poor semen quality may therefore not explain our findings.

There are limitations to our study, as 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, which has been suggested previously (25). Socioeconomic factors are likely to have been important for referral patterns, especially in the early study period (1960–1979), when infertility

Table 3. Age- and Period-adjusted Standardized Mortality Ratios and 95% Confidence Intervals by Cause of Death Among 43,277 Danish Men Without Azospermia Referred to the Copenhagen Sperm Analysis Laboratory for Infertility Between 1963 and 2001 According to Sperm Concentration^a

Cause of Death	No. of Deaths	Standardized Mortality Ratio	95% Confidence Interval
Infectious diseases including tuberculosis	32	0.44	0.22, 0.90
Cancer	233	0.95	0.71, 1.26
Vascular diseases	55	0.60	0.33, 1.09
Cardiac disease	162	1.15	0.80, 1.65
All diseases of the respiratory organs (including bronchitis, emphysema, and asthma)	24	1.29	0.49, 3.41
All diseases of the digestive organs (including cirrhosis of the liver, gall bladder diseases)	120	1.04	0.72, 1.50
Diseases of the urogenital organs	6	1.10	0.07, 18.5
Suicide and accidents	211	0.81	0.59, 1.10
Other causes of death	260	0.80	0.61, 1.04

^a Reference group, <20 million/mL.

treatment was not an integrated part of the established health-care system. In the National Danish Birth Cohort, the participation rate was less than 50%, but nevertheless selection bias was not estimated to greatly influence findings within the cohort (38), suggesting that findings even in selected cohorts may be generalized to the population at large.

We studied mortality in relation to semen quality but cannot ignore the fact that the men participating in our study, due to their higher socioeconomic status, are diagnosed earlier than men from the general population and therefore survive longer with their disease. Semen quality may thus not be a marker of general disease-free survival but of a longer survival with disease. We, however, compared semen quality among men within the cohort, and it is therefore less important whether they, in fact, represent the general population. Men referred because of vasectomy had decreased mortality, and men referred because of testicular cancer had increased mortality compared with the men referred because of infertility, suggesting that the data are valid. Men with azospermia were excluded, as this group consisted of a mixture of men with different diagnoses, and some of them had previously undergone vasectomy. Men with proven fertility before the azospermic sample was delivered had reduced mortality, whereas childless men with azospermia at delivery of the sample had increased mortality, suggesting that some men may have azospermia due to external factors (e.g., obstructions), thereby actually having normal testicular function despite the azospermia.

The follow-up was register based, and the men were not contacted. We did not, therefore, obtain information about lifestyle factors (smoking, alcohol intake, dietary and exer-

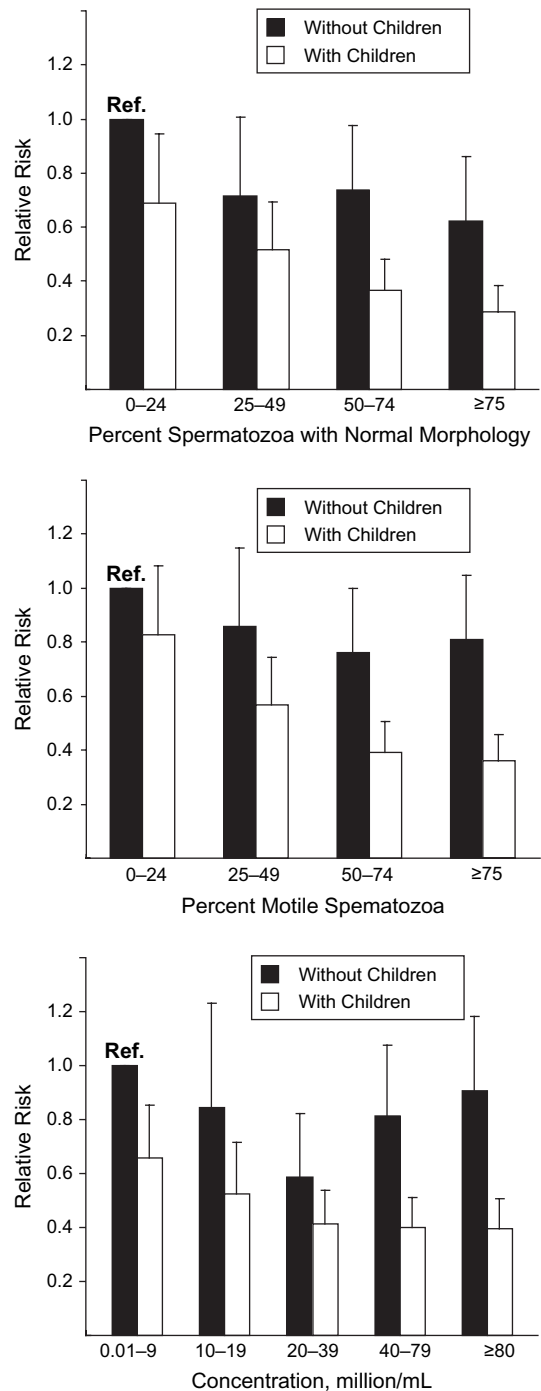


Figure 1. Relative risk of death according to fertility status and percent of sperm with normal morphology, percent motile spermatozoa, and sperm concentration among 43,277 Danish infertile men without azospermia referred to the Copenhagen Sperm Analysis Laboratory for infertility between 1963 and 2001. "Ref." indicates the reference group and includes men aged 50 years in 1980. Error bars represent 95% confidence intervals.

cise habits) related to mortality. However, mortality from causes related to lifestyle factors (respiratory diseases, cirrhosis, cardiovascular disease, and suicide) was not

significantly decreased among men with good semen quality, as these men had decreased mortality due to a wide range of diseases. In addition, we did not obtain information about socioeconomic factors and marital status, which have both been related to mortality. No studies have, however, to our knowledge, related these factors to semen quality, and the bias is therefore likely to be nondifferential, underestimating an effect of semen quality on mortality. In addition, no information was obtained regarding whether the man was, in fact, the biologic father of his children (adopted children were included) and whether some were conceived after infertility treatment. Thereby, some infertile men may have been misclassified as fertile. This is, however, likely to be a smaller proportion and not likely to have significantly affected our results; if so, however, it would underestimate our findings. Likewise, referred men with normal semen quality are likely to have had an infertile partner, which may increase the risk of divorce, thereby categorizing some fertile men as childless and underestimating the effect of fertility on mortality.

The testicular dysgenesis syndrome hypothesis suggests that in utero exposures determine later male reproductive health, including semen quality and the risk of testicular cancer (11). If the same intrauterine factors that affect the male reproductive system also influence late-life major disease occurrence and death, it may be expected that sperm quality is associated with male disease occurrence—in particular, cardiovascular disease—and survival. We did, indeed, observe an association between sperm quality and survival and, for several parameters, even a “dose-response pattern.” However, the increased mortality was due to a wide range of diseases and not particularly diseases related to the causes predicted by the fetal origins hypothesis (cardiovascular disease and diabetes (12)). The potential fetal influence on the male reproductive system, hence, seems to be different from the fetal factors associated with late-life disease occurrence, which is also supported by the controversial association between birth weight and sperm quality observed in most studies (39–41).

We therefore hypothesize that good semen quality may be a more general biomarker of overall health. A few other such biomarkers are known, for example, hand-grip strength in midlife, which is known to predict disability and survival up to 25 years later (42). For grip strength, a number of possible mechanisms can be suggested, as it is associated with overall muscle strength and cognitive functioning that are important predictors of survival among the elderly. In a recent short piece in *Science* (43), semen quality has been correlated with the intelligence quotient, thereby suggesting a “latent fitness factor” by which evolutionarily desirable traits, both physical and mental, may be correlated.

In conclusion, we found a decrease in mortality with increasing semen quality in a dose-response manner among more than 40,000 men visiting a sperm laboratory during a 40-year period. The decreased mortality was due to a broad range of diseases and not only related to lifestyle factors, thereby suggesting that the decreased mortality was not solely caused by differences in lifestyle. In addition, the association was found among both fertile and childless men, suggesting that the findings may not solely

be attributed to differences in social factors. We therefore speculate that good semen quality may be a fundamental biomarker of overall male health. This is, to our knowledge, the first study to document a relation between semen quality and subsequent mortality, and the finding needs to be replicated in other studies. Nevertheless, our study is large, and it is not likely to be repeated in the near future. In addition, the public health implication of semen quality as a fundamental biomarker of overall health is intriguing.

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