Male Infertility and Risk of Nonmalignant Chronic Diseases: A Systematic Review of the Epidemiological Evidence

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Abstract

The association between male infertility and increased risk of certain cancers is well studied. Less is known about the long-term risk of nonmalignant diseases in men with decreased fertility. A systemic literature review was performed on the epidemiologic evidence of male infertility as a precursor for increased risk of diabetes, cardiovascular diseases, and all-cause mortality. PubMed and Embase were searched from January 1, 1980, to September 1, 2016, to identify epidemiological studies reporting associations between male infertility and the outcomes of interest. Animal studies, case reports, reviews, studies not providing an accurate reference group, and studies including infertility due to vasectomy or malignancy were excluded. The literature search resulted in 2,485 references among which we identified seven articles fulfilling the eligibility criteria. Of these, four articles were prospective (three on risk of mortality, one on risk of chronic diseases) and three were cross-sectional relating male infertility to the Charlson Comorbidity Index. The current epidemiological evidence is compatible with an association between male infertility and risk of chronic disease and mortality, but the small number of prospective studies and insufficient adjustment of confounders preclude strong statements about male infertility as precursor of these outcomes.

Keywords
- male infertility
- comorbidity
- mortality
- chronic diseases

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In recent years, there has been an increasing interest in the association between male infertility and future health, especially the development of chronic diseases and mortality. Furthermore, emerging evidence suggests that a man's general and reproductive health is closely intertwined.[1] Although the link between male infertility and testicular cancer is well established, recent studies have shown that abnormal semen parameters may also be linked to nonmalignant diseases such as diabetes and ischemic heart disease.[2,3] It has been hypothesized that shared genetic pathways including hormones as well as environment and lifestyle factors possibly acting *in utero* could play an important role.[4,5] Furthermore, studies have suggested that semen quality may serve as a biological marker for future male health.[6] The latter representing results from large epidemiological studies in Europe and the United States which have found an association between poor semen quality and mortality.[6–8]

Infertility is a disease of the reproductive system defined as the failure to achieve a clinical pregnancy after at least 1 year of regular unprotected sexual intercourse.[9] The lifetime prevalence of infertility is between 16 and 25%, where male factor etiology is identified in 30 to 50% of the cases.[10,11] Male infertility is often associated with semen abnormalities and a semen analysis is used as a measure of male fecundity.[12] A conventional semen analysis includes sperm count, motility, and morphology and is today routine care for diagnosis of male infertility. Determinants of sperm quality and other semen characteristics include age, onset of puberty, body mass, stress, and lifestyle conditions such as smoking and alcohol, but wide intra-variability in semen quality is also observed in the same men.[13–17] Decreasing trends in semen quality have been reported over the past decades, but the evidence is still debated.[18–20] Despite intensifying research on male reproductive health, still much is unknown as no clear explanation of the underlying causes of male infertility is identified in at least 30 to 50% of cases.[10]

According to the World Health Organization (WHO), the three main nonmalignant chronic diseases include diabetes, cardiovascular disease, and respiratory disease.[21] Cardiovascular diseases include a broad group of diseases affecting the heart and blood vessels and are the leading cause of death globally.[22] Diabetes is a group of metabolic diseases characterized by high blood sugar levels, with increasing trends reported globally. Infertile men may have lower levels of testosterone,[23] which has previously been linked to risk of cardiovascular disease, diabetes, and mortality.[24,25] Chronic respiratory diseases include diseases of the airway and lungs but are excluded from this review as the pathogenic pathways connecting to reproduction are uncertain.[26]

Since the introduction of in vitro fertilization (IVF) with intracytoplasmic sperm injection (ICSI) in 1992,[27] even men with severe fertility problems are able to become biological fathers. Thus, in many cases, the investigation of the male partner includes only semen analysis without further investigation. This is a source of concern, as an underlying medical pathology may be the cause of the infertility linking this to increased risk of disease or mortality in later life.[28] It should be kept in mind that, in contrast to women, men are not subjects of regular health screening programs; therefore, the contact with the health care system as part of infertility workup may represent a golden opportunity to identify subjects being at increased risk of long-term morbidity and mortality and to offer them proper preventive measures.

During the past decade, the association between a man's reproductive and general health has, therefore, received increased attention in Europe and the United States. But despite this, the association remains unclear and there is a need for a systematic assessment of this evidence. The objective of this review was to systematically identify and evaluate the existing epidemiological evidence linking male infertility to subsequent risk of morbidity and mortality.

Methods

We reviewed the literature according to the MOOSE guidelines for systematic reviews of observational studies[29] with methodology adapted from Bonde et al.[30]

Protocol and Registration

A review protocol has been registered at PROSPERO.org with registration number CRD42016047463, prior initiation of the review process on September 9, 2016, with amendments regarding inclusion of cross-sectional studies on October 15, 2016. All authors approved the final version of this protocol.

Eligibility Criteria

We conducted a systematic search of peer-reviewed original articles in English published between January 1, 1980, and September 1, 2016, to identify articles providing data on the association between male infertility and the risk of the two out of three major nonmalignant chronic conditions according to WHO (diabetes and cardiovascular diseases) and all-cause mortality. The complete search specification is available from the corresponding author.

Eligibility criteria for inclusion in the systematic review were as follows:

1. *Exposure*: A population (cohort or case–control study) of infertile men where the fertility diagnosis precedes the outcome of interest (cf. point 2). According to the amendments in PROSPERO protocol, we also included cross-sectional studies relating infertility to outcomes of interest (cf. point 2), as they supported the mechanistic relationships we try to assess using the included prospective studies.
2. *Outcomes*:
   a. Diabetes: Type 1 and type 2 diabetes according to the International Classification of Diseases (ICD). These were defined as ICD8 249, 250, and ICD10 E10, E11, E13, E14, or by using self-reported questionnaires.
   b. Cardiovascular diseases: Hypertensive disease, ischemic heart disease, pulmonary disease, and cerebrovascular diseases defined as ICD8 400–404, 410–414, 420–429, and ICD10 I10–I15, I20–I26, I63–65, I70, or using self-reported questionnaires.
   c. All-cause mortality provided by death records.

We included epidemiological studies where the exposure and outcome is provided by medical health records, national health registries, or self-reported questionnaire data. Exclusion criteria were as follows: (1) animal studies, (2) studies where male infertility was due to malignancy or vasectomy, (3) studies not written in English, (4) no adequate reference group, (5) case stories, (6) reviews, and (7) not original or duplicate publications.

Search and Study Selection

The PubMed and Embase databases were searched for articles that combined medical subject headings (MeSH) or text words for the exposure male infertility and the disease outcomes. Two authors (C.H.G. and E.V.B.) sifted through titles and abstracts and retrieved 26 articles for full-text reading. To ensure that all relevant literature was identified, we also conducted hand searches through bibliographies from recent studies and authors who have published within this field. Any disagreements during the article selection were resolved by a third author (J.P.B.).

Data Extraction

For each study, the following descriptive characteristics were extracted and summarized in ►**Table 1**: (1) reference, (2) location where the study took place, (3) study population, (4) study design, (7) study size, (8) outcome ascertainment, (8) comparison groups, (9) main findings, and (10) adjusted confounders.

Quality Appraisal

To evaluate the quality of the articles included in our review, we used a modified version of the completeness of reporting scoring system by Bonzini et al that is commonly used in epidemiological studies.[31] The completeness of reporting was evaluated using a seven-point scale with the following criteria: (1) study design, (2) sampling frame and procedures, (3) inclusion/exclusion criteria, (4) main characteristics of the study population, (5) method(s) of exposure assessment, (6) method(s) of outcome assessment, and (7) methods of statistical analysis. Two pairs of authors independently assigned scores to the articles and later met to compare, thoroughly discuss, and resolve any discrepancies regarding their independent scores of each individual article. A score of 1/0 was given if the criteria were fulfilled/not fulfilled.

Bias and Confounding

Potential risk of bias and confounding was assessed using a predefined list of seven items adapted from validated checklists relevant for the articles identified for this review,[32] including (1) reporting of tested hypothesis; (2) sample size justification, small numbers of cases, or exposed may increase risk of false-negative reporting; (3) selection bias, related to seeking treatment for infertility; (4) information bias, outcomes identified by patient recall/questionnaires or by nonblinded medical interview; (5) confounding, failure to account for major potential confounders such as smoking and obesity,[14] is expected to bias estimates unpredictably even though we acknowledge that obesity might also have a mediating effect on infertility, for instance the effect of testosterone deficiency leading to obesity which thus leads to disease; (6) measuring of confounding; and (7) exposure contrast, studies using no contrast in semen quality counts and only considering yes/no infertile would bias results toward null because of insufficient exposure contrast.

After sifting and rating articles, there was consensus among all reviewing authors that articles relating male infertility to the Charlson Comorbidity Index (CCI) should be included (three articles). CCI was originally developed by Charlson et al[33] and includes 19 major disease categories, including cardiovascular, pulmonary, ulcer, and liver diseases as well as dementia, diabetes, renal disease, cancer, and AIDS. Each disease is scored according to severity (score: 1–6) and comorbidity is summed to an index which is used in medicine and epidemiology as an estimate of disease burden and correlated to risk of mortality. Although the specific diseases of our interest are included in CCI, we were unable to gather details on which diseases contributed to the CCI scores reported in the included articles, but importantly CCI is strongly correlated with mortality risk, relevant in this review.[33–35]

Results

Our database searches generated 2,481 hits published after 1980 after the removal of duplicates and 4 additional articles were identified via hand searches (cf. ►**Fig. 1**). In total, nine articles were rated and two were later excluded as they did not comply with our PROSPERO inclusion criteria. Of the remaining seven articles, four directly explored risk of chronic diseases/mortality as an outcome of infertility, while the remaining three explored male infertility in relation to the CCI. The data extracted was separated into three categories/themes: "general health status measured by CCI," "risk of chronic disease," and "risk of mortality." The results are presented in ►**Table 1**.

General Health Status Measured by CCI

The first study to use CCI scores as a measure of general health for infertile men was the study by Salonia et al in 2009.[36] In this cross-sectional study of 637 participants, infertile men (regardless of the infertility cause) had significantly higher mean CCI scores compared with their fertile controls (0.33 vs. 0.14, $p < 0.001$). The analysis was adjusted for age, body mass index (BMI), and educational status. More recently, Eisenberg et al investigated the relationship between semen production and medical comorbidity in a population of 9,387 men evaluated for infertility in 2015. In this study, the authors stratified the cohort of infertile men according to CCI and reported that higher CCI was associated with impaired semen parameters.[37] The analysis was adjusted for age and year of evaluation. Also in 2015, an Italian study similarly found a positive association between CCI and semen parameters in a group of 2,100 infertile men after adjustment for age, BMI, and length of infertility.[38]

Risk of Chronic Disease

The only study to specifically explore incident diabetes/cardiovascular disease after a diagnosis of male infertility

Table 1 Characteristics and results of epidemiological studies on male infertility and future health

Reference	Location	Population	Study design	Study size	Outcome ascertainment	Comparison groups	Main findings	Adjusted confounders	CR[a]	Bias[b]
Eisenberg et al (2015)	United States	Men evaluated for infertility between 2001 and 2009 identified from inpatient and outpatient insurance claim	Cohort study	115,986	Diagnosis codes identified on inpatient and outpatient claims	Men with a diagnosis of infertility were compared with (1) men undergoing only infertility testing without a diagnosis of infertility and (2) men with vasectomy	An increased risk of diabetes HR 1.30 (95% CI: 1.10–1.53) and ischemic heart disease HR 1.48 (95% CI: 1.19–1.84) was reported among infertile men	Age, year of evaluation, follow-up time, outpatient visits, smoking, and obesity	6	3
Eisenberg et al (2015)	United States	Men evaluated for infertility between 1994 and 2011 identified in an infertility semen database	Cross-sectional	9,387	Administrative data containing ICD-9 codes.	Men were stratified according to CCI and semen quality was compared across groups	Men with a higher CCI had lower semen volume, concentration, motility, total sperm count, and morphology scores	Age, year of evaluation	6	4
Ventimiglia et al (2015)	Italy	Men evaluated for infertility between 2005 and 2014	Cross-sectional	2,100	Self-reported medical history	Men were stratified into groups according to CCI and semen quality and other health parameters were compared across groups	Sperm concentration decreased as CCI increased and a higher rate of oligospermia and nonobstructive azoospermia was observed in patients with CCI $\geq$1	Age, BMI, and length of infertility	6	6
Eisenberg et al (2014)	United States	Men evaluated for infertility identified from an infertility semen database (1994–2011) and an andrology database (1989–2009)	Cohort study	11,935	National health registry data	Comparisons of men with sperm concentration <15 million/mL to men with a sperm concentration of >15 million/mL.	Men with more semen abnormalities had higher risk of death	Age, year of evaluation, and general health at baseline	6	3
Salonia et al (2009)	Italy	Men evaluated for infertility between 2006 and 2007 and hospital controls	Cross-sectional	637	Self-reported medical history	Men identified with male factor infertility and age-comparable controls recruited from hospital advertisements	Infertile men had significantly higher mean CCI scores compared with their fertile controls	Age, BMI, and educational status	6	7
Jensen et al (2009)	Denmark	Men referred to the Copenhagen Sperm Analysis Laboratory for evaluation of semen quality between 1963 and 2001	Cohort study	43,277	National health registry data	Comparison of men with sperm concentration < 20 million/mL with a sperm concentration of >20 million/mL.	Mortality decreased as the semen quality increased up to a threshold of 40 million/mL, thereafter no additional effect was observed	Age and period	6	3
Groos et al (2006)	Germany	Hospital based: Marburg University Hospital between 1949 and onward	Cohort study	601	Medical records	Men were classified into three groups depending on their sperm count: normospermic (>20 million/mL), oligozoospermic (<20 million/mL and azoospermic men	A twofold higher risk of mortality was observed for oligospermic compared with normospermic men OR 2.19 (95% CI: 1.31–3.67) but only for men born between 1892 and 1937	Life expectancy at birth, age at examination, and socioeconomic status	3	10

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index.
[a]Completeness of reporting (CR): on a scale from 0 (low completeness) to 7 (high completeness).
[b]Bias and confounding: 1 = higher risk of bias, 0 = lower risk of bias.

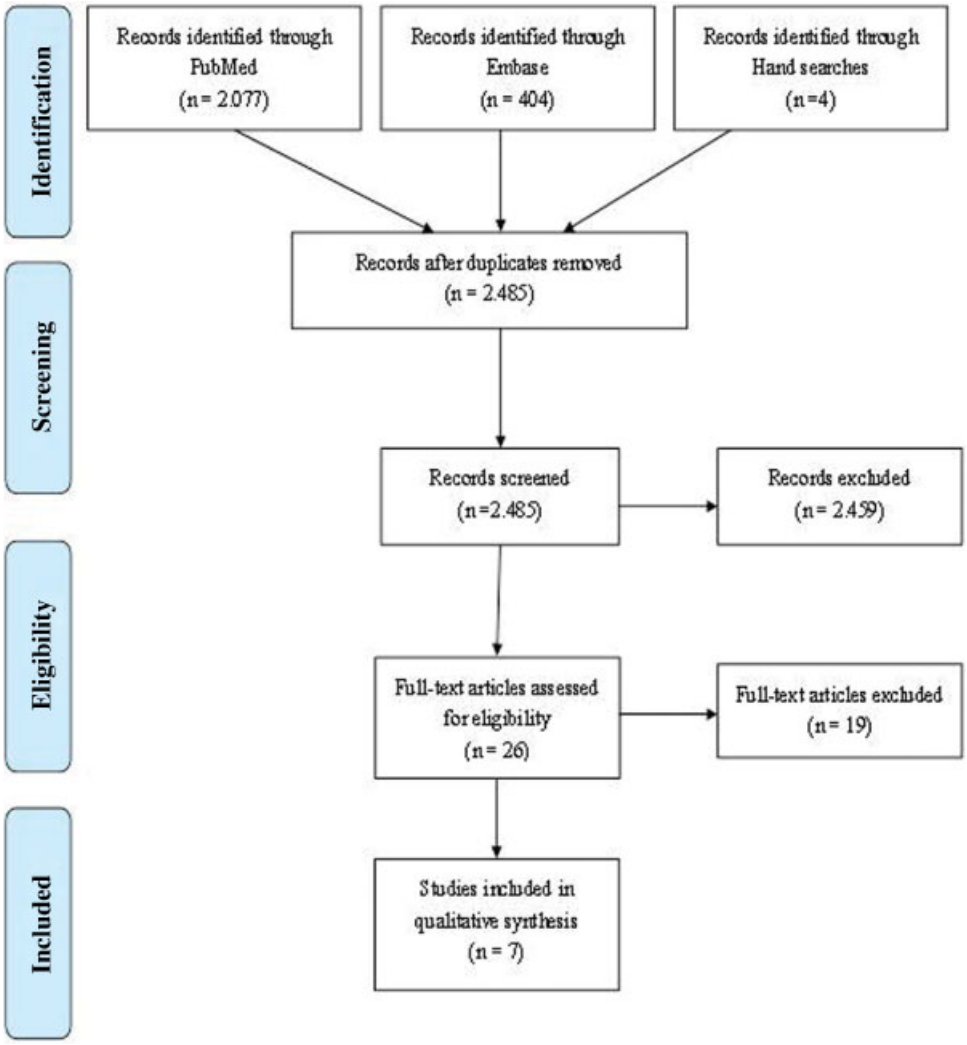

Fig. 1 Flow diagram showing results of the systematic literature to identify peer-reviewed articles addressing the association between male infertility and risk of diabetes, cardiovascular disease, and mortality.

was the one by Eisenberg et al in 2015.[2] Using insurance claims data, a group of men with a diagnosis of infertility were compared with, first, men undergoing only fertility testing, but without a diagnosis of infertility and, second, vasectomized men assumed to be biologically fertile. The researchers found a 30% increased risk of diabetes (hazard ratio [HR]: 1.30, 95% confidence interval [CI]: 1.10–1.53) and 48% increased risk of ischemic heart disease (HR: 1.48, 95% CI: 1.19–1.84) with a mean follow-up time of 3.28 years for the infertile men. The analyses were adjusted for age, year of evaluation, follow-up time, outpatient visits, smoking, and obesity.

Risk of Mortality

We identified three studies investigating the association between male infertility and risk of mortality, all of which reported positive associations. The first study to explore this area was that of Groos et al from Germany in 2006.[8] They used medical records of 601 men who had undergone an andrological evaluation at the University Hospital in Marburg from 1950 and onward. Using Cox regression, more than twofold higher risk of mortality was observed for oligospermic compared with normospermic men (OR: 2.19; 95% CI: 1.31–3.67) but only for men born between 1892 and 1931. No association was found in the younger birth cohorts. The analysis was adjusted for life expectancy at birth, age at examination, and socioeconomic status. The mean follow-up time was not reported. Three years later, a large register-based study from Denmark analyzed semen samples from 43,277 between 1963 and 2001.[6] Linkages were made to the National Death Register using unique personal identification numbers. Using standardized mortality ratios (SMRs), mortality decreased as sperm concentration increased up to a threshold of 40 million/mL. For instance, men with a sperm concentration of 10 to 19.99 million/mL had an SMR of 0.79 (95% CI: 0.63–0.99) compared with an SMR of 0.64 (95% CI: 0.54–0.76) for men with a sperm concentration between 40 and 79.99 million/mL. The analysis was adjusted for age as well as birth cohort and these men were followed up for up to 40 years. Finally, a study from the United States calculated HR in a cohort of 11,935 men evaluated for infertility between 1994 and 2009.[7] They found

that men with more semen abnormalities had a higher risk of death within a mean follow-up period of 7.7 years. For example, compared with men with normal semen quality, those with two or more semen abnormalities had a 2.57 higher risk (95% CI: 1.26–5.23) of death even after adjusting for age, year of evaluation, and baseline health.

Quality Assessment of the Studies

Nine articles were assessed for quality, but only seven articles were included in this review. Sample sizes were all high (number of participants between 600 and 116,000) and all studies took place in Europe or the United States. Most studies were register based or self-reported and compared normospermic with oligospermic men. Although most articles scored high in terms of completeness of reporting (six out of seven studies had score $\geq$6 on the seven-point score), the quality of the research was sometimes constrained by methodological issues and risk of bias, particularly for the cross-sectional studies. The major sources of bias were recall bias provided by questionnaires and insufficient adjustment for confounders (e.g., smoking and BMI). Both of these variables are established potential confounders.[14,39,40] Even though obesity might, in some cases, mediate the association between infertility and development of disease, low testosterone is a key hormone in the pathology of obesity[41] and obesity in turn is a key factor in many chronic diseases. Studies using administrative/register-based data were generally rated as having higher quality with less risk of bias.

Discussion

This is the first systematic review to assess the association between male infertility and risk of diabetes, cardiovascular disease, and mortality. These qualitative results are based on a rigorous and standardized evaluation of the available literature on this topic. Our overall conclusions are based on quality assessment of two groups of author-pairs to limit the risk of bias. Large epidemiological data are difficult to obtain in most countries, as outcomes may not be systematically recorded in central national registries and only men actively seeking fertility treatment receive a diagnosis. Furthermore, the outcomes of interest in this review are uncommon in men who are of reproductive age, thus requiring extensive longitudinal follow-up. Although our search generated 2,485 hits, only seven studies met our inclusion criteria and are included in this review. The included studies support the hypothesis of an association between male infertility and reduced general health and increased risk of mortality. Our aim was to identify studies that specifically explored the disease outcome or mortality as a direct consequence of male infertility. However, three of the included studies were cross-sectional, relating infertility to the CCI index as a measure of overall disease burden at a specific time point and without specifically identifying disease outcomes. These studies were included because the health indictor CCI is strongly correlated with mortality risk.[33–35] Only one article specifically explored male infertility and incidence of several chronic conditions, but none solely explored the risk of either cardiovascular disease or diabetes.

Since the introduction of ICSI, men with very poor semen quality were able to achieve biological fatherhood. As assisted reproductive technology advanced, several studies have focused on the adverse health outcomes of the mothers and children, while less attention has been paid to the fathers, especially in terms of nonmalignant disease risks.[2,42–45] On the other hand, the relationship between male infertility and cancer risk is more thoroughly investigated. Large studies from the United States and Europe have found associations between male infertility and risk of testicular cancer,[3] while conflicting results exists for the risk of prostate cancer.[46,47] More recently, male infertility was found to be a risk factor for several other cancers, including non-Hodgkin's lymphoma.[48]

A link between adverse male reproductive function on one hand and morbidity and mortality on the other hand may be explained in several ways, including (1) male infertility leading to poor health, for instance through mental stress related to the experience of infertility or testosterone deficiency; (2) poor general health leading to male infertility; and (3) a common "root" etiology including shared genetic origins or lifestyle factors causing both male infertility and poor general health. However, these categories are dynamic and will overlap in some cases.

Importantly, it should be noted that the populations used to assess this link are couples wanting children. Thus, we expect that a social element not detected in the included studies may play a role, in that some men not being able to have children are less prone to seek medical advice due to fear of discovering symptoms of disease or simply because they pay less attention to their own health status as they have no responsibilities or obligation for their own family.

Male Infertility Leading to Poor General Health

The precise etiology of a direct link between male infertility and poor health is not clear. However, infertility is often associated with negative psychological consequences including stress, depression, and anxiety.[49,50] These factors can all be related to stress hormone release, and prolonged stress is a risk factor for several diseases, particularly among men already predisposed.[51] Some studies have suggested that stressful events (such as undergoing fertility treatment) might affect the onset of diabetes or even death.[52,53] Importantly, stress may also be a causative factor in male infertility. However, its effects on spermatogenesis and testicular function is not fully understood.[54] Men with fertility problems also generally have lower levels of endogenous testosterone which has previously been linked to diabetes, cardiovascular disease, and mortality, although conflicting results exist.[55–57]

Poor General Health Leading to Male Infertility

If male infertility is indeed a predictor of future health, as suggested by the studies mentioned earlier, could we consequently assume that infertility and disease risk are directly associated?[58] Diabetes, in particular, may affect male reproductive function, via effects of endocrine control on spermatogenesis or erectile dysfunction, and diabetes is a well-established cause of male sexual dysfunction, which

may cause infertility. In addition, studies have shown that diabetic men have higher levels of DNA damage to their sperm which may also affect fertility.[59] However, genetically defective sperm has also been linked to increasing age trends of fatherhood.[60,61] As observed from the cross-sectional studies, men with fertility problems, although relatively young, already at the time of infertility investigation have increased prevalence of morbidities. This is also supported from a recent study showing that men with sperm concentrations below 20 million/mL have less favorable metabolic status and lower bone density, in the presence of low testosterone levels.[62]

Common Genetic Etiology and External Factors

Among men with severe oligospermia or azoospermia, genetic abnormalities may be present in some cases.[63] A recent review found 168 common genes significantly associated with both male infertility and disease mechanisms including ribosome and proteasome pathways.[4] These pathways seem to regulate processes important for human diseases such as metabolic and degenerative diseases. In addition, infertile men sometimes lack certain regulatory genes responsible for cell cycle control mechanisms, which ultimately could lead to increased risk of chronic diseases (and cancer).[1,64] Lastly, male infertility and chronic diseases/mortality share risk factors, such as smoking and adiposity, which may also explain the underlying association. A recent systematical review with meta-analysis concluded that BMI was associated with male infertility,[14] but a recent study by Bandel et al[65] reported no association between BMI and semen parameters among randomly selected men not seeking fertility treatment, while yet another study of Danish military conscripts reported that both low BMI and high BMI were associated with reduced semen quality.[66]

Quality of the Studies

The completeness of reporting was generally high. Only one study by Groos et al was of lower quality, as this group failed to account for the method used for sperm counts and generally reported unclear results.[8] Extrapolation of results from individual studies included in this review is also difficult; for example, one of the reviewed studies included men from a post-war period where the impact of environmental factors may have skewed the results making them difficult to extrapolate to situations today.[8] Generally, the included studies used internal reference groups, comparing semen quality of normo- and oligospermic men which is preferred as the risk of selection bias is reduced; however, we know today that this may be associated with some misclassification, as men with normal sperm counts may have DNA damage in sperm. One study compared men referred for *any type* of male infertility to hospital controls, which is a risky comparison as vasectomized men may be misclassified as "infertile."[36] Overall, the studies using administrative/register-based data were of higher quality and less risk of bias. Only one study adjusted for smoking.

Importantly, studies from Denmark and the United States have shown that men evaluated for infertility seem to be healthier than the general population.[6,7] This may be explained by a "healthy patient" effect, as men burdened by a severe medical problem may be less likely to start a family.

Strengths and Limitations of This Review

Although this systematic review has several strengths including the rigorous/standardized literature search and the quality assessment performed by two sets of independent researcher-pairs, this article does have some limitations. First, only seven studies were eligible for inclusion in this review, all of which found positive associations, which could imply potential publication bias. Second, the reports within this research area are largely directed by three research groups in the United States (three studies), Denmark (one study), and Italy (two studies); thus, although the review is based on a systematical review of current literature, our assessment of the area is largely influenced by selected scientists, which cannot be ignored. Due to the heterogeneity of the results, a meta-analysis was not possible.

Conclusion

Evidence relating the long-term health associated with male infertility is sparse and only seven studies were identified in this review, all supporting the association between male infertility and poor general health and risk of mortality. Uncertainty still remains regarding this association, and although infertility may indeed be the causal factor for disease later in life, alternatively a man's health status may impact semen quality which ultimately affects semen production and future disease risk. Almost half of the included studies in this review are cross-sectional and future studies should include a longer follow-up time and adjust for important confounders such as smoking.

Authors' Roles

Clara Helene Glazer and Elvira Vaclavik Braüner conceived the study, sifted titles and abstracts, and independently included and excluded articles. Clara Helene Glazer, Elvira Vaclavik Braüner, Katia Keglberg Hærvig, and Ditte Vassard reviewed and rated the individual articles. All authors contributed to the design and provided critical feedback. Susie Rimborg completed the systematic literature search. Clara Helene Glazer drafted the manuscript to which all authors contributed and approved the final version.

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