Submitted: 17 December, 2025 Accepted: 03 April, 2026 Published: 30 June, 2026 DOI:10.22514/jomh.2026.046

REVIEW

JOMH
Journal of Men's Health

Semen as a marker of a man's overall health

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Abstract

Semen analysis is traditionally used to assess male fertility but has limited application beyond reproductive evaluation. Emerging evidence suggests that abnormal semen parameters may serve as indicators of broader health risks extending beyond fertility. Multiple studies have demonstrated associations between impaired semen quality or infertility and increased risks of sexual dysfunction, cancer, and chronic disease. Collectively, these findings highlight the potential for semen analysis to shed light beyond exclusive fertility assessment, and to provide broader insight into measures of a man's long-term health. This review aims to summarize current evidence of the relationship between semen parameters with long-term health outcomes, and to evaluate the potential role of semen analysis as a screening tool for men's overall health. Literature was sourced from PubMed and Scopus with an emphasis on articles published between 2020–2025. Keywords used included "Semen analysis", "Infertility", "Cancer", and "Chronic Disease". Only full-length texts from peer reviewed sources were included. Abnormal semen parameters have been associated with higher rates of erectile dysfunction, premature ejaculation, and reduced libido. Men with infertility or impaired semen quality demonstrate increased risks of testicular and prostate cancers, as well as other malignancies. Beyond oncologic outcomes, infertile men are associated with higher incidences of hyperlipidemia, renal disease, and chronic pulmonary disease, and are more likely to develop diabetes, ischemic heart disease, and substance use disorders. Furthermore, abnormal semen parameters have been associated with increased all-cause mortality. Although abnormal semen parameters may not represent early manifestations of chronic disease, men with infertility or impaired semen quality appear to be more susceptible to various health conditions. Semen analysis performed during fertility evaluation may therefore provide valuable insight into a man's overall health and potential long-term health risks, facilitating early detection and intervention.

Keywords

Semen analysis; Infertility; Sexual function; Cancer; Chronic disease

1. Introduction

Semen analysis (SA) is a cornerstone of male fertility assessment and evaluates multiple physical and functional characteristics of semen, including semen volume, total sperm number, sperm motility, morphology, and vitality [1]. Abnormalities such as oligozoospermia (reduced sperm count), azoospermia (absence of sperm in the ejaculate) [2], asthenozoospermia (reduced motility) [3] or teratozoospermia (abnormal morphology) [4] may reflect disruption in spermatogenesis, spermiogenesis, epididymal storage or sperm maturation. These characteristics can provide information about the general "quality" of a man's sperm and help estimate the probability of spontaneous conception (Fig. 1).

Infertility is defined as the failure to conceive naturally after at least 12 months of regular unprotected intercourse by the International Classification of Diseases (ICD-11) [5]. Male factor infertility reflects disruption in a complex system that can result from a wide array of intrinsic or extrinsic forces. Many associations with exogenous disruption of semen quality (SQ) have been observed, though causal mechanistic effect remains uncertain. Choudhury *et al.* [6], identify decreased total sperm count and normal sperm morphology with men who smoke cigarettes. The investigators attribute this association with disruption of reproductive regulation but do not identify exactly how cigarettes impact SQ. Similarly, Liu *et al.* [7], identifies air pollutants such as ozone, carbon monoxide, nitric dioxide, sulfur dioxide, and particulate matter to all contribute to associated adverse effects on semen volume, sperm concentration, and motility. Still, no direct mechanism is identified. A Danish study identified a similar association between sugar sweetened beverages (SSB) with decreased sperm concentration and total sperm count as well as hormonal disruptions [8]. Though limited in its ability to draw causality,

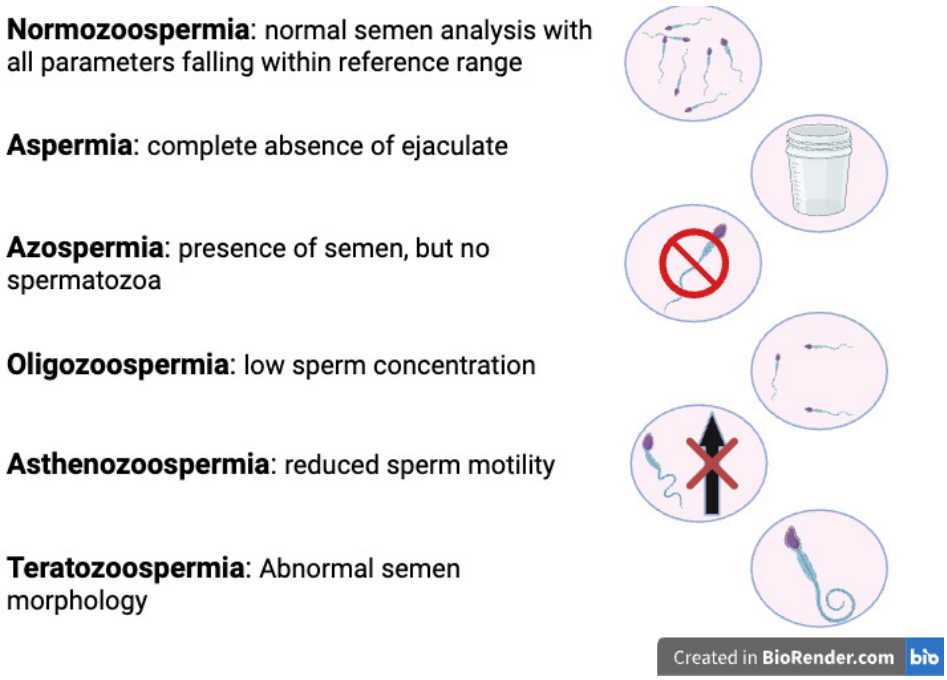

FIGURE 1. Common semen abnormalities.

this study further supports the growing body of evidence that SSBs have direct suppressive effects on testicular function. The role of environmental exposures is often discussed within the context of their contribution to greater amounts of reactive oxygen species (ROS), which have consistently been recognized as mediators of sperm dysfunction [9]. Exposure to lifestyle toxins or environmental pollutants can result in systemic increases in ROS, which can contribute to the pathogenesis of systemic disease in all tissues. However, the limited repair mechanisms of spermatozoa make them particularly vulnerable to ROS exposure.

Other sources of ROS can result from natural biologic processes like response to infection. Leukocytospermia (LCS), or presence of leukocytes in semen, is a direct marker of inflammation or infection in the male genitourinary tract, even in the absence of other symptoms. Leukocytes are known to be significant sources of ROS, thus LCS represent one of the largest categories of potentially treatable causes of sperm abnormalities [10]. LCS has been reported both in the presence and absence of sexually transmitted infections [11]. Additionally, the presence of LCS was associated with reductions in SQ independent of detectable infection [11]. Similarly, bacteriospermia in men with chronic prostatitis represents another marker of genitourinary inflammation and has been associated with impairments in SQ, likely due to increased oxidative damage [12].

In addition to exogenous factors, or internal biologic processes, substantial evidence of several genetic etiologies of SQ disruption exists. Kleinfelter syndrome is the most common sex chromosome anomaly in infertile men and most commonly presents with a 47 XXY karyotype, though a minority of patients may exhibit 46 XY/47 XXY mosaicism [13]. Mosaic patients may exhibit less severe oligozoospermic phenotypes, however the most common genotype presents with non-obstructive azoospermia [13]. Recent studies have identified other genes associated with non-obstructive azoospermia including *Azoospermia Factor c* (*AZFc*) [14], nuclear receptor subfamily 5 group A member 1 (*NR5A1*) and androgen receptor variants [15] which are associated with azoospermia or severe oligospermia. These genetic variants reflect intrinsic abnormalities with sperm production or maturation and have less to do with sperm dysfunction due to environmental factors like ROS. While these genetic conditions underscore the intrinsic biologic underpinnings of severe SQ impairment, much of the epidemiologic literature examining downstream health outcomes does not directly measure specific semen parameter (SP) abnormalities. Instead, many large-scale population studies rely on clinical infertility diagnoses or fertility status as surrogate markers of impaired semen quality. This methodological distinction is important, as the precision afforded by genetically and phenotypically characterized semen abnormalities contrasts sharply with the indirect nature of proxy-based classifications.

In many epidemiological contexts where detailed SA data are unavailable, fertility status is used as a proxy for semen impairment. However, infertility is an indirect and imprecise surrogate for SQ. It may reflect couple-level dynamics, relationship status, healthcare access, or behavioral factors. By definition, infertility excludes men who are not sexually active, who are not attempting conception, or who have been trying for less than 12 months, thereby potentially omitting substantial segments of the population with abnormal SP. Accordingly, reliance on infertility as a proxy introduces exposure misclassification and complicates efforts to establish causal relationships or to validate SA as screening tools for broader health outcomes.

Direct SA offers a more granular and biologically informative point of assessment than proxy measures. Specific abnormalities may provide insight into underlying endocrinologic or structural pathology. Oligozoospermia may reflect

hypogonadism or broader gonadal dysfunction [16], whereas azoospermia can be further categorized into obstructive and non-obstructive etiologies [2]. In contrast, fertility status or fatherhood status alone do not distinguish between these mechanistic pathways. Historically, SA has been used primarily to evaluate male reproductive potential. However, emerging research raises the possibility that abnormal SP may be associated with systemic health outcomes beyond reproduction [17]. Observational studies have reported associations between abnormal SP and increased risks of certain malignancies [18] as well as metabolic dysfunction [19], cardiovascular disease [19], and autoimmune disorders [20]. Importantly, these relationships are associative and derived largely from observational data; they do not establish causation. Abnormal SP may represent markers of underlying systemic vulnerability rather than direct contributors to disease pathogenesis. Nonetheless, SA may hold potential as a broader indicator of male physiologic health. If future longitudinal studies confirm consistent associations across specific semen abnormalities and defined health outcomes, SP could provide a unique opportunity for earlier identification of men at elevated risk for chronic disease. At present, however, careful interpretation is warranted, and further prospective investigation is necessary to clarify temporal relationships and underlying mechanisms.

2. Materials and methods

This narrative review was conducted between October 2025 and February 2026. The review prioritized peer-reviewed literature published in English, with particular emphasis on studies published within the preceding three years (2022–2025) to ensure inclusion of the most current data. Search strategies incorporated combinations of controlled vocabulary with key terms including: “Semen Analysis”, “Chronic Disease”, “Diabetes Type II”, “Metabolic Syndrome”, “Prostate Cancer”, “Testicular Cancer”, “Familial Cancer”, “Oligozoospermia”, “Azoospermia”, “Teratozoospermia”, “Aspermia”, “Asthenozoospermia”, “Reactive Oxygen Species”.

Inclusion criteria consisted of human studies, original research articles, review articles, and investigations reporting objective semen parameters or functional sperm outcomes. Editorials, animal studies, conference abstracts without full manuscripts, and non-peer reviewed sources were excluded. Titles and abstracts were screened for relevance, followed by full-text review of selected articles. Given the narrative design, formal systematic review methodology was not employed. Instead, studies were qualitatively synthesized and grouped thematically with emphasis placed on sample size, recency of publication and clinical relevance when selecting studies for inclusion.

3. Results and discussion

3.1 Association of abnormal semen parameters with sexual dysfunction

Abnormalities in SP appear to extend beyond impaired fertility and may reflect broader disturbances in male sexual health. Evidence suggests that SQ is closely associated with several domains of sexual function, underscoring its potential value as a biomarker of overall reproductive and sexual well-being. In a cohort study of 448 men, Lotti *et al*. [21] examined the relationship between semen parameter impairment, or “infertility severity”, and sexual dysfunction. Even prior to stratification by SP, men classified as infertile demonstrated significantly higher rates of erectile dysfunction (ED) (18.3% *vs.* 0%; $p = 0.006$) and premature ejaculation (PE) (12.9% *vs.* 4.1%; $p = 0.036$) compared with fertile controls. Importantly, the prevalence of ED increased in a stepwise fashion with worsening SQ, demonstrating a graded association between the severity of spermatogenic impairment and erectile function ($p < 0.0001$). This relationship persisted despite comparable hormonal profiles, glycometabolic parameters and penile vascular measures between groups, suggesting that conventional organic contributors to ED did not fully account for the observed differences. Men with azoospermia exhibited the most profound sexual dysfunction, followed sequentially by those with at least one abnormal SP, normozoospermic infertile men, and fertile controls ($p < 0.0001$). Similar dose-response relationships were observed for PE and diminished libido. Azoospermic men demonstrated the highest rates of PE ($p < 0.0001$), reduced ejaculatory latency, impaired libido, and decreased orgasmic function relative to fertile counterparts (all $p < 0.05$). Although infertility status is not synonymous with abnormal SP, the study’s findings support the use of infertility classification as an initial surrogate for semen impairment. The subsequent demonstration of progressively worsening sexual dysfunction with increasing severity of semen abnormalities strengthens the inference that declining SQ is independently associated with deteriorations in male sexual function.

A recent meta-analysis by Liu *et al*. [22] further reinforces the observed relationship between male infertility and sexual dysfunction. Across pooled studies, the designation of male infertility was consistently associated with lower scores in multiple domains of sexual function, with erectile dysfunction, orgasmic function and sexual desire demonstrating the most pronounced differences. Although the analysis did not stratify findings according to specific SP, infertility status was significantly correlated with reductions in International Index of Erectile Function (IIEF) scores. Infertile men exhibited lower erectile function scores (Standard mean deviation (SMD) = −0.29, 95% Confidence Interval (CI) = −0.53 to −0.05, $p = 0.02$), as well as diminished orgasmic function (SMD = 0.48, 95% CI = −0.95 to −0.01, $p = 0.04$) and reduced sexual desire (SMD = −0.68, 95% CI = −1.20 to −0.15, $p = 0.01$). These findings further characterize infertility as a clinical state that is consistently associated with multidimensional impairments in sexual function. While the analysis does not establish directionality or causation, the reproducibility of these associations across studies supports a relational link between infertility status and broader disturbances in male sexual health.

Extending the observed associations between SQ and sexual function to clinically distinct populations further illustrates the broader relational implications of impaired spermatogenesis. In cohorts of couples affected by pregnancy loss (PL), men with specific semen abnormalities demonstrated a higher prevalence of ED relative to normozoospermic counterparts. Elevated sperm DNA fragmentation (SDF) (Odds ratio (OR):

2.75; CI: 1.49–5.09; $p = 0.001$), isolated teratozoospermia (OR: 2.44; CI: 1.22–5.31; $p = 0.024$) and the presence of two or more abnormal SP (OR: 2.65; CI: 1.45–4.86; $p = 0.002$) were each associated with increased odds of ED [23]. Complementary findings have been reported in related PL cohorts, in which men within the lowest IIEF score range (5–11) exhibited the most pronounced impairments in SQ, including reduced progressive motility, abnormal morphology, and elevated SDF ($p < 0.002$, $p < 0.001$, $p < 0.003$, respectively) [24]. These graded associations between sexual dysfunction severity and semen abnormalities further support a relational link between deteriorating spermatogenic parameters and compromised sexual function. Importantly, these investigators did not attempt to ascribe pregnancy loss directly to sperm quality. However, the authors noted that their study populations exhibited higher rates of semen abnormalities than typically observed in the general population and therefore the potential contribution of suboptimal SP could not be excluded. Collectively, these data suggest that while spontaneous conception may still occur in men with impaired SQ, broader reproductive outcomes may also demonstrate associations with underlying semen abnormalities.

The available evidence suggests that the higher prevalence of sexual dysfunction among infertile men and those with impaired SP likely reflects a complex interplay of somatic health factors and psychological burden. Across diverse populations, a consistent, graded association emerges between worsening SQ and impairments in erectile function, libido, orgasmic function, and ejaculatory parameters. Although current literature does not establish a definitive mechanistic pathway linking abnormal SP with sexual dysfunction, the reproducibility of these associations across independent studies supports a meaningful relational connection. Rather than representing isolated reproductive abnormalities, impaired SP may serve as clinical markers associated with broader dimensions of male sexual health.

3.2 Association of abnormal semen parameters with cancer

A growing body of literature has identified associations between impaired SP and malignancy. In the case of testicular cancer, these observations suggest a complex and potentially bidirectional relationship in which spermatogenesis and oncologic risk may coexist within the same clinical populations. Men diagnosed with testicular cancer have been observed to demonstrate compromised SQ at presentation. An early controlled study reported significantly lower sperm concentration ($p < 0.01$) and total sperm count ($p < 0.01$) in men with testicular cancer compared to both patients with malignant lymphoma and healthy controls [25]. A recent retrospective study reinforces the association between testicular cancer and impaired SQ. In this small cohort of 38, 18% of participants had abnormally low semen volume, 47% demonstrated oligozoospermia and 24% demonstrated asthenozoospermia [26]. Notably, SP remained largely unchanged across disease progression from stage I to stages II/II, suggesting that the presence of testicular cancer itself may not directly disrupt spermatogenesis.

Conversely, poor SQ has been associated with higher subsequent incidences of testicular cancer. In a small Japanese cohort of 272 men presenting with azoospermia between 2020 and 2021, 1.8% were incidentally found to harbor testicular tumors [27]. While limited by small sample size, the study highlights the observed co-occurrence of severe spermatogenic impairment and malignancy. Larger retrospective analyses further support this relationship. In a cohort of 20,433 men undergoing SA, undergoing evaluation itself was independently associated with an elevated incidence of testicular cancer. Stratification by SQ demonstrated particularly strong associations among oligozoospermic men based on sperm concentration and total count (Hazard ratio (HR) 11.9 and 10.3, respectively). Additionally, men in the lowest quartiles for motility, viability, morphology, and total motile count exhibited increased hazard ratios for subsequent testicular cancer (HR 4.1, 6.6, 4.2, 6.9 respectively) [28]. These findings suggest that more severe or multidimensional semen impairment is associated with greater oncologic risk.

Similar patterns have been observed in larger cohorts of men diagnosed with infertility. In a large retrospective study of 51,461, those seeking fertility treatment demonstrated a modestly elevated incidence of testicular cancer (Standard incidence ratio (SIR): 1.3, CI: 0.9–1.9), while men with confirmed male factor infertility exhibited substantially higher risk estimates (SIR: 2.8, CI: 1.5–4.8) [29]. Beyond affected individuals themselves, familial clustering has also been observed. Anderson *et al.* [30] reported that first degree relatives of men who had undergone SA exhibited a 52% increased risk of developing testicular cancer compared with relatives of healthy controls (HR: 1.52; CI: 1.05–2.22). This finding raises the possibility that shared genetic or developmental factors may underlie both impaired spermatogenesis and increased cancer susceptibility within families.

Compared to associations between impaired SP and subsequent risk of testicular malignancy, comparatively fewer investigations have examined the association between impaired SQ and the later development of prostate cancer. In a follow up analysis to their 2009 report, Walsh *et al.* [18] observed that men classified as infertile demonstrated a higher incidence of prostate cancer, with the strongest association observed for high grade disease (HR: 2.6; CI: 1.4–4.8). Similarly, a large Swedish cohort reported that men who achieved fatherhood through assisted reproductive technologies (ART) were at increased risk of early onset prostate cancer [31]. Specifically, conception via intracytoplasmic sperm injection (ICSI) was associated with elevated risk (HR: 1.64; CI: 1.25–2.15), as was *in vitro* fertilization (IVF) (HR: 1.33; CI: 1.06–1.66). IVF is commonly used for couples having trouble conceiving and encompasses a broad range of male and female etiologies. In contrast, ICSI is more frequently employed in cases of severe male-factor infertility, including oligozoospermia, asthenozoospermia, or azoospermia. Accordingly, use of ICSI may function as a proxy for more profound impairment in SP relative to conventional IVF. However, ART modality as a surrogate for severity of spermatogenic dysfunction carries important limitations. Treatment selection reflects not only SQ but also evolving clinical practices, socioeconomic considerations, and provider preference. The investigators appro-

priately acknowledged several important sources of selection bias. Men seeking ART services may differ systematically from the general population, tending to be older and more highly educated. Additionally, ART registries lack data on men who sought fertility services and did not result in successful fatherhood, representing potential exclusion of the most severe cases.

Consequently, ART utilization introduces the possibility of exposure misclassification and residual confounding when interpreted as a marker of impaired SQ, further limiting the extent to which ART use can reliably approximate underlying SP abnormalities. Despite these limitations, the large size of certain ART registries, along with the assumption that some degree of spermatological dysfunction is present among men seeking ART, provides support for their use as a proxy for impaired SQ. A meta-analysis of 10 studies evaluating the association of infertility with prostate cancer included investigations based on clinical infertility diagnoses or fatherhood status as a surrogate for fertility. Notably, none of the studies directly examined specific SP [32]. The results of this study was a wide array of heterogenous findings which could not conclude a definitive association between infertility and prostate cancer risk. The absence of studies directly assessing SA and reliance on proxies for SQ as well as the heterogeneity of results underscores a critical gap bridging reproductive and oncologic health.

Beyond the association with testicular and prostate malignancies, emerging evidence suggests that fertility status may be associated with broader hereditary cancer susceptibility. A retrospective study published in 2024 evaluated cancer risk among first-, second- and third-degree relatives of men with azoospermia or severe oligozoospermia compared with relatives of fertile controls [33]. Relatives of men with azoospermia demonstrated increased risks of bone and joint cancers, soft tissue malignancies, uterine cancer, Hodgkin lymphoma, and thyroid cancer. Relatives of men with severe oligozoospermia were reported to have elevated risks of bone and joint cancers, colon cancer, and testicular cancer. These findings raise the possibility that severe spermatogenic impairment may cluster within families affected by hereditary cancer susceptibility. However, the retrospective design, reliance on registry data, and potential for shared environmental or socioeconomic confounding limit causal inference. Additionally, while azoospermia and severe oligozoospermia represent more direct indicators of impaired SP than infertility diagnoses alone, they still encompass heterogeneous etiologies which may differentially relate to oncologic risk.

Further supporting a possible shared genetic basis, a 2025 study reported that men diagnosed with infertility had nearly a fivefold increased likelihood of harboring likely pathogenic or pathogenic germline variants in cancer-predisposition genes, most commonly *breast cancer 2* (*BRCA2*) and *Fanconi anemia*, *complementation group M* (*FANCM*) (OR: 4.7; CI: 1.81–15.5; $p = 2.3 \times 10^{-4}$) [34]. While these findings suggest overlap between infertility and hereditary cancer risk, they do not establish that abnormal SP themselves confer increased oncologic risk. More direct evidence linking severe spermatogenic dysfunction to cancer evidence was reported by Eisenberg *et al*. [35], who observed that men with azoospermia had an increased subsequent risk of developing cancer. Although azoospermia constitutes a defined semen abnormality, the study's retrospective design and reliance on clinical cohorts introduce potential ascertainment bias and residual confounding. As with prior studies, the observed associations do not demonstrate a causal relationship, and shared genetic, developmental, or environmental mechanisms may underlie both impaired spermatogenesis and cancer susceptibility. Extending this line of inquiry to more granular markers of sperm integrity, a cross-sectional study reported a positive correlation between SDF and familial cancer incidence [36]. The observed association between increasing degrees of SDF and a greater reported family history of malignancy may provide preliminary insight into potential mechanistic links between genomic instability in germ cells and inherited cancer risk. However, the cross-sectional nature to the study precludes determination of temporality or directionality. It remains unclear whether a familial predisposition to cancer contributes to higher rates of SDF, whether elevated SDF reflects an underlying heritable defect that also increases cancer susceptibility, or whether both phenomena arise from a separate, shared biologic process. As such, these findings should be interpreted as hypothesis-generating rather than causal.

Taken together, existing evidence relies heavily on indirect markers of male reproductive dysfunction, rather than objective SP, and even studies evaluating defined abnormalities such as azoospermia often do not stratify risk according to graded severity of SP impairment. Compared with other domains of men's health, such as sexual function, there is a relative paucity of research systematically examining cancer risk across the spectrum of specific SA abnormalities. Accordingly, while existing findings warrant further investigation, they should be interpreted as associative rather than causal. Prospective studies incorporating standardized SA data and careful stratification by parameter type and severity are needed to clarify whether abnormal SP independently predict long-term cancer risk or instead reflect shared underlying biologic vulnerabilities.

3.3 Association of abnormal semen parameters with other diseases

Accumulating evidence suggests that men with impaired SP are at an increased burden of chronic health conditions. In a retrospective analysis derived from a prospectively maintained database, Ferlin *et al*. [16] reported that, at the time of SA, men with oligozoospermia had higher body mass index, waist circumference, blood pressure, lipid levels, and homeostatic model assessment (HOMA) index values, as well as a greater prevalence of metabolic syndrome. Importantly, these findings reflect cross-sectional associations observed at presentation and therefore do not establish temporal directionality or causation.

In a retrospective study, Eisenberg *et al*. [37] reported that men diagnosed with male factor infertility had an increased risk of later developing diabetes mellitus (HR: 1.30; CI: 1.10–1.53), ischemic heart disease (HR: 1.48; CI: 1.18–1.84), alcohol abuse (HR: 1.48; CI: 1.07–2.05) and drug abuse (HR: 1.67; CI: 1.06–2.63) compared with men merely presenting

for a fertility consultation. Although increased incidence of hyperlipidemia, renal disease and chronic pulmonary disease was observed among infertile men, these associations did not reach statistical significance. The authors emphasized that these findings demonstrate association rather than causation and postulated that shared genetic or biologic pathways may underlie both reproductive and systemic health, noting that approximately 10% of the male genome is involved in reproductive function [38]. As such, further investigation into the association with diabetes reports male factor infertility as an independent predictor of subsequent type II diabetes mellitus [39]. In one investigation, increasing severity of semen impairment was associated with progressively higher risk of developing diabetes. Specifically, men with oligozoospermia (HR: 1.44; CI: 1.01–2.06), azoospermia (HR: 2.1; CI: 1.25–3.56) and aspermia (HR: 3.20; CI: 1.00–10.31) demonstrated incrementally elevated risks compared with men without these diagnoses. Although this graded association may suggest a relationship between severity of SP abnormality and metabolic risk, residual confounding and shared underlying pathophysiology cannot be excluded, and these data do not establish a causal pathway.

A 2017 claims-based analysis study found that men coded as infertile had higher risks of developing autoimmune disorders compared with vasectomized men, including systemic lupus erythematosus (HR: 3.11; CI: 2.00–4.86), rheumatoid arthritis (HR: 1.56; CI: 1.19–2.05), psoriasis (HR: 1.28; CI: 1.09–1.50), multiple sclerosis (HR: 1.91, CI: 1.10–3.31), and Grave's disease (HR: 1.46, CI: 1.10–1.92) [40]. Vasectomized men were selected as a comparator group under the assumption that they represented proven fertility and shared demographic characteristics with men seeking fertility evaluation. However, infertility status in this context was based on diagnostic coding and does not directly measure SQ. While the absolute risk of autoimmune disease remained low, the observed associations suggest that male infertility diagnoses may cluster with systemic immune dysregulation. However, the heterogeneity of autoimmune conditions observed makes a single unifying biologic mechanism unlikely.

In another study, fatherhood status was used as a proxy for male fertility, with childlessness presumed to reflect reduced reproductive potential [41]. Childless men were found to have less favorable metabolic profiles and higher risks of cardiovascular disease and all-cause mortality compared with fathers. However, childlessness is an especially imprecise surrogate for impaired SP, as it may reflect personal choice, partner factors, relationship status, socioeconomic conditions, or female infertility. The authors acknowledged that the childless cohort had lower educational attainment and a high proportion of unmarried men, highlighting the potential for substantial confounding. Fatherhood status does not directly measure spermatogenic function and should be interpreted cautiously when used as a marker of fertility status or SQ.

More direct evaluation of SP was performed in a retrospective cohort study of men undergoing infertility evaluation, which found that men with abnormalities in semen volume, sperm concentration, motility, total sperm count, or total motile sperm count had higher risks of mortality compared with men with normal SP [42]. Notably, men with two or more abnormal SP demonstrated a 2.3-fold increased risk of death (CI: 1.25–4.65). Although these findings align more closely with objective semen abnormalities of interest, the retrospective design and potential for selection bias limit causal interpretation. Again, much of the available literature relies on proxy measures of assumed impaired SQ, and even studies incorporating abnormal SA are observational in nature. Prospective investigations incorporating standardized semen assessments and longitudinal follow up are needed to clarify the temporal and biologic relationships between SQ and long-term health outcomes. Table 1 (Ref. [18, 21–23, 29–31, 34, 37, 39, 40, 42]) summarizes the reported associations between abnormal SP and various long-term health outcomes discussed in this review. Given that much of the evidence is derived from observational studies, many of which lack longitudinal follow up and do not evaluate SA as a validated screening tool, these relationships should be interpreted as associative. They do not establish causality and should be considered within the context of the methodological limitations described above (Table 1).

4. Conclusion

SA remains a well-established and invaluable tool for evaluating male reproductive potential. Beyond its role in assessing fertility, there is increasing interest in the body of evidence suggesting that abnormal SP may be associated with an elevated risk of long-term health conditions. However, much of the current literature is derived from cross-sectional and retrospective studies, and therefore causality cannot be inferred. Furthermore, the lack of longitudinal data further prevents the utility of SA as a screening or predictive tool in any other context other than in reproductive settings. Future research should prioritize longitudinal study designs and incorporate greater granularity in the assessment of SQ, including severity and specific type of abnormality, rather than relying solely on binary categorizations of fertile versus infertile. Additionally, the use of existing SA registries to investigate associations with non-reproductive health outcomes remains limited. While proxy measures of SQ buttress some of the findings derived directly from SA data, they also constrain the strength and scope of the conclusions that can be drawn. While proxies for infertility, such as treatment seeking behavior or childlessness, can provide useful insights in population-based studies, they are inherently limited in capturing true spermatogenic dysfunction and should not be interpreted as direct measures of SQ. Despite these limitations, clinicians should remain attentive to the potential long term health risks among men with impaired SP. Abnormal SQ may serve as an early indicator of broader systemic vulnerability, underscoring the importance of holistic health assessment and preventative care throughout the lifespan of these patients.

TABLE 1. Health associations with semen abnormalities and male infertility.

Clinical Association	Associated Risk	Reference
Sexual Dysfunction		
Infertile men, relative to fertile controls, demonstrate higher rates of erectile dysfunction	OR = 16.67	[21]*
Infertile men, relative to fertile controls, demonstrate higher rates of premature ejaculation	OR = 3.57	[21]*
Infertility is associated with lower IIEF scores in the erectile function domain compared to healthy controls	SMD = −0.29	[22]
Infertility is associated with lower IIEF scores in the orgasmic function domain compared to healthy controls	SMD = −0.48	[22]
Infertility is associated with lower IIEF scores in the sexual desire domain compared to healthy controls	SMD = −0.68	[22]
Men with high sperm DNA fragmentation demonstrate a higher prevalence of erectile dysfunction compared to normozoospermic men	OR = 2.75	[23]
Malignancy		
Men being evaluated for infertility are at a higher risk of developing testicular cancer compared to healthy controls	SIR = 1.3	[29]
Men with known diagnosis of infertility demonstrate higher risk of developing testicular cancer compared to controls	SIR = 2.8	[29]
First degree relatives of infertile men have an increased risk of developing testicular cancer relative to healthy controls	HR = 1.52	[30]
Infertile men are more likely to develop high grade prostate cancer	HR = 2.6	[18]
Men who achieved fatherhood through intracytoplasmic sperm injection demonstrate a higher risk of developing early onset prostate cancer	HR = 1.64	[31]
Men who achieved fatherhood through *in-vitro* fertilization demonstrate a higher risk of developing early onset prostate cancer	HR = 1.33	[31]
Infertile men demonstrate an increased incidence of pathogenic gene or pathogenic germline gene variants related to hereditary cancer (*Breast cancer 2* (*BRCA1*) and *Fanconi anemia*, *complementation group M* (*FANCM*) most frequent)	OR = 4.7	[34]
Chronic Disease		
Infertile men are at an increased risk of developing diabetes mellitus II when compared to men simply presenting for an infertility consultation	HR = 1.30	[37]
Infertile men are at an increased risk of developing ischemic heart disease when compared to men simply presenting for an infertility consultation	HR = 1.48	[37]
Infertile men are at an increased risk of developing alcohol abuse disorder when compared to men simply presenting for an infertility consultation	HR = 1.48	[37]
Infertile men are at an increased risk of developing drug abuse disorder when compared to men simply presenting for an infertility consultation	HR = 1.67	[37]
Men with oligozoospermia have an increased risk of developing diabetes mellitus II compared to controls	HR = 1.44	[39]
Men with azoospermia have an increased risk of developing diabetes mellitus II compared to controls	HR = 2.1	[39]

TABLE 1. Continued.

Clinical Association	Associated Risk	Reference
Chronic Disease		
Men with aspermia have an increased risk of developing diabetes mellitus II compared to controls	HR = 3.20	[39]
Infertile men are more likely to develop general autoimmune disease (including systemic lupus erythematous (SLE)) compared to vasectomized men	HR = 3.11	[40]
Infertile men are more likely to develop rheumatoid arthritis compared to vasectomized men	HR = 1.56	[40]
Infertile men are more likely to develop psoriasis compared to vasectomized men	HR = 1.28	[40]
Infertile men are more likely to develop multiple sclerosis compared to vasectomized men	HR = 1.91	[40]
Infertile men are more likely to develop Grave's disease compared to vasectomized men	HR = 1.46	[40]
Men with two or more semen abnormalities are at an increased risk for all-cause mortality	HR = 2.29	[42]

*Findings reported as odds ratio (OR), standard mean difference (SMD), standardized incidence ratio (SIR), or hazard ratio (HR) as presented in the original studies. The International Index of Erectile Function 5 (IIEF-5) is a validated, patient reported, five item questionnaire (score range 5–25) used to assess severity of erectile dysfunction. *Lotti et al. [21] reported an odds ratio (OR) of 0.06 [0.01–0.46] comparing the odds of ED in fertile men vs. infertile men, indicating substantially lower odds in fertile men. For consistency with the direction used throughout this review, describing the odds of ED in infertile men relative to fertile men, the inverse of the reported odds ratio and confidence interval was used in our summary table (OR = 16.67 [2.2–100]).*

AVAILABILITY OF DATA AND MATERIALS

All data analyzed and reviewed in this article are derived from publicly available sources.

AUTHOR CONTRIBUTIONS

MK—conceptualization and design. EM—writing-original draft preparation; interpreting of materials. EF—writing–review and editing. BH—writing–review and editing. All authors read and approved the final manuscript. All authors have reviewed and approved of author contributions.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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How to cite this article: Ethan McGonagle, Evan Farrel, Beatriz Hernandez, Mohit Khera. Semen as a marker of a man's overall health. Journal of Men's Health. 2026; 22(6): 1-9. doi: 10.22514/jomh.2026.046.