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Editorial commentary

Spermatozoa as harbingers of mortality: the curious link between semen quality and life expectancy

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Introduction

This edition of *Human Reproduction* features an important publication highlighting the curious dose-dependent relationship that exists between semen quality and life expectancy in men (Priskorn *et al.*, 2025). According to these extensive Danish data, if your total motile sperm count is $<5 \times 10^6$/ml you can expect to live for 77.6 years, whereas if you are lucky enough to possess a count of $>120 \times 10^6$/ml, your life expectancy will increase to 80.3 years. This is encouraging for those so endowed, although they will still be dying 3 years before their female partner. A characteristic feature of our species that, depending on your perspective, might be considered one of the great inequalities of creation or an indication of the Creator's capacity for intelligent design, is that women live longer than men. This gender difference in mortality is present throughout the life course and, in 2021, amounted to an average 5-year discrepancy in global life expectancy that was observed, to varying degrees, in every nation on the planet (Dattani and Rodés-Guirao, 2023). Such observations raise important questions about the major determinants of life expectancy and just how they are impacted by gender and reproductive fitness. A complex array of factors is thought to be involved in determining longevity in our species, including genetic or epigenetic mutations, endocrine milieu, vulnerability to disease, environmental pollution, lifestyle choices, diet, risky behaviours, occupational hazards, the availability of social support networks, the periodic outbreak of war, and the sweep of global pandemics—all of which impact men and women differently.

The general notion that reproductive fitness reflects the overall health trajectory of a given individual has been advanced before (Choy and Eisenberg, 2018; Burke *et al.*, 2022), and not just for men. In women, pregnancy-related complications such as preeclampsia, gestational hypertension, and gestational diabetes are thought to predict an individual's subsequent risk of cardiovascular disease and renal failure, while lactation is associated with long-term protection against cancer and type II diabetes (Victora *et al.*, 2016; Tobias *et al.*, 2017; Turbeville and Sasser, 2020). In men, it appears to be their semen profile that is providing the most significant information concerning their future health and wellbeing (Priskorn *et al.*, 2025). This differs from previous large-scale population-based studies which have indicated an inconsistent relationship between male infertility and subsequent health (Lundberg *et al.*, 2019; Del Giudice *et al.*, 2020). Thus, the semen profile seems to be providing critical quantitative information on male health that is beyond the reach of a generalized infertility diagnosis, which is clearly compromised by its binary nature and inherent imprecision.

So, if spermatozoa really are the canaries in the coal mine of male health, the obvious question to ask is, why? What possible factors could link the ultimate life expectancy of males with the quality of their semen profile in early adulthood. Are the causative factors unique to men or reflective of some fundamental pathological process that is driving fertility and mortality in both males and females, but at different rates? This commentary sets out to explore this question.

The importance of genetics

One obvious gender difference that might be relevant to life expectancy is that men only have one X- chromosome, while women have two. As a consequence, we see a preponderance of recessive X-linked conditions in men such as haemophilia, Duchenne muscular dystrophy, red-green colour blindness, Fragile X syndrome, and X-linked agammaglobulinemia. For some of these X-linked pathologies, we see a clear link between poor semen quality and reduced longevity, as in the case of Klinefelter syndrome or Kennedy disease (Punjani and Lamb, 2020). However, these well-defined genetic conditions are relatively rare and cannot account for the population-wide trends revealed by Priskorn *et al.* (2025). Much more likely is that poor semen quality and mortality are linked to complex patterns of recessive genetic (and epigenetic) variation on the X-chromosome, not just single gene defects.

During evolution, the X-chromosome has accumulated many genes linked to spermatogenesis with the result that X-chromosome genetic variants are thought to drive male infertility in several species including man, mice, and cattle (Wang and Pan, 2007; Zheng *et al.*, 2010; Krausz *et al.*, 2012; Fortes *et al.*, 2020; Vockel *et al.*, 2021). In addition, the X-chromosome has also been implicated as a cause of mortality at all stages of life. For example, it has been suggested that recessive X-linked mutations are responsible for the preponderance of male mortality at the time

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of birth and during infancy (Mage and Donner, 2004). Later in life, the X-linked mutations responsible for Brugada syndrome are associated with a preponderance of sudden cardiac deaths in young and middle-aged men (Jellins *et al.*, 2013). We also know that mutations in the X-linked serotonin 2C receptor are associated with sudden epileptic deaths in males (Massey *et al.*, 2021). So, the signs are clearly there; genetic variants on the X-chromosome could reasonably impact both semen quality and male mortality.

In this context, we should also not forget the Y-chromosome. This chromosome is obviously unique to the male genome and has a well-recognized influence on semen quality. Indeed, mutations on the Y-chromosome are thought to be the most common genetic cause of poor semen quality and male infertility (Colaco and Modi, 2018; Aitken and Baker, 2020). Importantly, recent studies have also demonstrated important roles for Y-encoded genes in multiple domains of male health, including cancer and neuropsychiatric conditions (Colaco and Modi, 2018; Dirican and Nelson, 2024). So, this chromosome might also be contributing to the genetic links between impaired semen quality and male mortality.

The importance of the immune system

Another gender-related difference that affects both reproductive competence and life expectancy, centres on the superiority of the female immune system compared with its male counterpart. This difference is thought to reflect an evolutionary investment in the ability of women to maintain pregnancy and accomplish the most delicate of immunological juggling acts, permitting tolerance of the foetal allograft while ensuring the latter's protection against all forms of infectious disease (Mariencheck, 2024). Males have not made as heavy an investment in their immune system and, as a result, exhibit higher infection rates than females for a variety of bacterial, viral, and parasitic pathogens (Shepherd *et al.*, 2021). As an illustration, during the COVID-19 (COronaVIrus Disease of 2019) pandemic, the death rate was 10–20% higher for men than for women (Torres *et al.*, 2023). In the last quartile of life, death rates rise steeply from a variety of conditions that have an immunological basis, including respiratory diseases, cardiovascular conditions, infections, cancers, and autoimmunity, all of which have a higher prevalence, and generally induce greater mortality, in males than females. Is it therefore possible, that such immunological failures are not only responsible for the untimely mortality of men in their golden years but also architects of poor semen quality decades earlier?

In many ways, the tolerance and protection of isogenic spermatozoa in men, is similar to the foetal-allograft-acceptance conundrum in women. Successful sperm production and maturation involve striking an appropriate immunological balance that protects millions of isogenic spermatozoa from immunological attack while summarily rejecting any pathogenic microbe in the immediate vicinity (Zhao *et al.*, 2020). Failure of this system at the testicular and epididymal levels is known to result in profound changes to the number and quality of spermatozoa available for ejaculation (Jrad-Lamine *et al.*, 2011; Chereshnev *et al.*, 2021). So, it is entirely conceivable that male mortality is heralded by infertility in early adulthood due to poor immunological regulation of the reproductive process, including the generation of anti-sperm antibodies, the presence of which is known to be associated with defects in the semen profile (Cui *et al.*, 2015).

Support for this concept has come in a recent publication focusing on the immunological status of infertile men (Amodio *et al.*, 2025). In this study, phenotypic profiling revealed an increased frequency of myeloid cells and inflammatory mediators in the seminal fluid and peripheral blood of infertile male patients. In addition, single-cell RNA sequencing of peripheral blood T cells revealed a signature of 'exhaustion' in oligo-astheno-teratozoospermic patients and of 'senescence' in cases of non-obstructive azoospermia. While these young males may have been otherwise healthy at the time of semen analysis, their proinflammatory immunological state provides a clear mechanism for the appearance of devastating comorbidities later in life.

Importance of comorbidities

While the associations between mortality and semen quality observed by Priskorn *et al.* (2025) were not explained by disease registered at the time of semen evaluation, it is possible that disease was present but not detected when the semen profile was constructed, or that the comorbidity arose in its aftermath. Testicular cancer, for example, is a condition that might not have been diagnosed at the time of semen analysis and yet has a profound effect on the number and quality of ejaculated spermatozoa (Aitken, 2022; Thomas, 2023). However, because this condition is mercifully rare, it cannot readily explain population-wide differences in life expectancy. More relevant to the Priskorn argument might be life-threatening 'incident' comorbidities that arise after the semen analysis has been performed but feature an aetiology that is shared with the determinants of semen quality. Included in this category are conditions considered autoimmune (rheumatoid arthritis, multiple sclerosis, lupus, Graves' disease, Hashimoto disease, psoriasis), cardiovascular (heart disease, hyperlipidaemia, hypertension, peripheral vascular disease), metabolic (diabetes mellitus, liver disease), and oncological (testicular, prostate). Significantly, if males are stratified according to the severity of their semen abnormalities, those with the poorest sperm parameters exhibit the highest risk of a comorbidity diagnosis later in life (Burke *et al.*, 2022).

Environmental and lifestyle factors

In addition to intrinsic genetic, immunological and disease-related factors, environmental pollution, and lifestyle may also make a dynamic contribution to the link between semen quality and male mortality. In this context, an important observation is that the difference between male and female mortality rates has not remained constant with the passage of time (Zarulli *et al.*, 2021). For example, in European countries like the UK and France, the difference in male and female life expectancy increased dramatically in the 1950's and 60's but then underwent a progressive reversal (Dattani and Rodés-Guirao, 2023). One explanation for this trend is that it has been significantly affected by smoking. During the Second World War, heavy smoking was largely a male habit fostered by the military's decision to supply its soldiers with free cigarettes in an attempt to boost their morale. In the years that followed the armistice, cigarette consumption contributed to a large number of male deaths as a result of cancer and cardiovascular disease. In recent years, the overall uptake of smoking has declined and, in concert, the difference between male and female life expectancy has narrowed (Zarulli *et al.*, 2021). Given the detrimental impact that smoking has on semen quality (Osadchuk *et al.*, 2023), it is reasonable to propose that a lifetime's dedication to this habit could have negatively affected semen quality in males of reproductive age, while facilitating their passage to the afterlife as the years advanced. Other

lifestyle factors such as obesity or exposure to mobile phone radiation, could also potentially account for the combination of poor semen quality and reduced life expectancy (Wang *et al.*, 2021; Zhang *et al.*, 2022), although neither obesity nor mobile phone use are predominately male attributes.

In addition to lifestyle factors, exposure to a wide range of environmental pollutants is also known to impair semen quality (Wu *et al.*, 2024) and could feasibly generate mortality later in life as a consequence of persistent exposure (Naidu *et al.*, 2021). One notable mechanism by which pollutants might achieve such a dual action would be to attack the telomeres that adorn the tips of every chromosome and ensure the latter's integrity during repeated rounds of replication. Short telomere length is associated with early ageing and the premature onset of age-related diseases, as well as impaired spermatogenesis (Yang *et al.*, 2018; Liu *et al.*, 2021). Since telomere length is a paternally inherited trait (Moazamian *et al.*, 2022), it is certainly plausible that an attack on the telomeres of the father's spermatozoa could result in the combination of reduced semen quality and shortened life expectancy in the male offspring as highlighted by Priskorn *et al.* (2025). Although this may not seem to account for sexual dimorphism in longevity, females do tend to have longer telomeres than males, in keeping with the established relationship between telomere length and lifespan (Barrett and Richardson, 2011). The reason for this is that females appear to be better equipped to look after their telomeres by virtue of an X-linked gene encoding dyskerin, a known regulator of telomerase activity (Lansdorp, 2022). Thus, while all the progeny of affected fathers may inherit shortened telomeres, female embryos have an enhanced capacity to repair the telomeric damage before it has an opportunity to impact their health trajectory—or their fertility (Rocca *et al.*, 2019).

An overarching hypothesis

As is often the case with landmark publications, the article by Priskorn *et al.* (2025) poses more questions than it answers. In establishing a proportional link between life expectancy and semen quality, this paper is providing important clues in relation to the fundamental mechanisms regulating fertility and mortality. In this commentary, I have highlighted several potential mediators of such an association including genetic defects on the sex chromosomes (X or Y), a compromised immune system, comorbidities, lifestyle factors, and chemical pollutants capable of compromising telomeric integrity. Given the complexity of these factors, we might ask whether they are acting independently, or do they reflect the existence of some fundamental pathological process that cuts across all of these epidemiological pathways? If so, what is this process, and to what extent can it account for both the link between semen quality and life expectancy and gender-related differences in longevity?

The following hypothesis is based on the principle that both semen quality and longevity are vulnerable to oxidative attack. Free radical-mediated cellular damage has long been known to influence semen quality (Jones *et al.*, 1979; Aitken and Clarkson, 1987; Pasqualotto *et al.*, 2008) and oxidative stress is central to the free radical theory of ageing (Ashok and Ali, 1999). Free radicals are also powerful inducers of DNA damage and the formation of *de novo* mutations. Although an oxidative attack could theoretically target any part of the genome, oxidatively-induced recessive mutations on the X- and Y-chromosomes are particularly relevant to the observed impacts on semen quality and longevity, due to their genomic isolation in males. Oxidative stress is also known to accompany the dysregulation of the immune system and the generation of a pro-inflammatory state that accompanies both poor semen quality and reduced longevity (La Vignera *et al.*, 2013; Teissier *et al.*, 2022). Many of the incident co-morbidities that are associated with poor semen quality including autoimmunity, cardiovascular disease, and metabolic dysregulation are also associated with oxidative stress and the induction of free radical-mediated damage (Burke *et al.*, 2022). Lifestyle factors that influence both semen quality and life expectancy, such as obesity and smoking, are similarly associated with a state of redox imbalance (Aitken, 2018), as are many of the environmental chemicals that are known to impair male reproductive health (Mustafa *et al.*, 2022). The high number of guanine residues in telomeres also renders these structures particularly vulnerable to oxidative damage and the telomere shortening associated with poor semen quality and reduced male longevity. So, any factor (genetic, immunological, metabolic, environmental, or lifestyle) that enhances overall levels of oxidative stress, could reasonably be expected to drive changes in the semen profile and subsequent patterns of mortality, as observed by Priskorn *et al.* (2025). Furthermore, an aetiology grounded in oxidative stress might also explain the relationships observed between complications of pregnancy (preeclampsia, gestational hypertension, and gestational diabetes) and female mortality later in life (Theilen *et al.*, 2018). An overarching oxidative stress hypothesis also accords with the observation that circulating antioxidant levels are generally higher in women than men, just as their telomeres are usually longer (Allegra *et al.*, 2023; Tiberi *et al.*, 2023). So perhaps, for both genders, the secret to achieving both high fecundity and heathy ageing, is to monitor oxidative stress and adopt measures to maintain a balanced redox state. Could it be that simple? Clearly, much food for thought.

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