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Timeless or tainted? The effects of male ageing on seminal fluid

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Reproductive ageing can occur due to the deterioration of both the soma and germline. In males, it has mostly been studied with respect to age-related changes in sperm. However, the somatic component of the ejaculate, seminal fluid, is also essential for maintaining reproductive function. Whilst we know that seminal fluid proteins (SFPs) are required for male reproductive success across diverse taxa, age-related changes in SFP quantity and composition are little understood. Additionally, only few studies have explored the reproductive ageing of the tissues that produce SFPs, and the resulting reproductive outcomes. Here we provide a systematic review of studies addressing how advancing male age affects the production and properties of seminal fluid, in particular SFPs and oxidative stress, highlighting many open questions and generating new hypotheses for further research. We additionally discuss how declines in function of different components of seminal fluid, such as SFPs and antioxidants, could contribute to age-related loss of reproductive ability. Overall, we find evidence that ageing results in increased oxidative stress in seminal fluid and a decrease in the abundance of various SFPs. These results suggest that seminal fluid contributes towards important age-related changes influencing male reproduction. Thus, it is essential to study this mostly ignored component of the ejaculate to understand male reproductive ageing, and its consequences for sexual selection and paternal age effects on offspring.

KEYWORDS

senescence, reproduction, ejaculates, seminal fluid, germline, oxidative damage, seminal fluid proteins

1. Introduction

Ageing is the time-dependent decline of an organism's biological function (Monaghan et al., 2008), leading to reduced physiological abilities and ultimately death. Ageing results in numerous biological changes that include telomere shortening, accumulation of somatic mutations, loss of proteostasis, mitochondrial dysfunction, and disruption of nutrient sensing pathways (Charlesworth, 1993; Kirkwood, 2005; López-Otín et al., 2013). Organisms also tend to have a lower reproductive output at older compared to younger ages. However, the onset and rate of decline in female fertility varies considerably across taxa, depending on life-history strategies and ecologies of species (e.g., Lemaître et al., 2020b; Campos et al., 2022), making it difficult to generalise patterns of ageing across the tree of life (Jones et al., 2014).

Onset and rate of age-related biological decline and impaired reproductive function varies between males and females (Bronikowski et al., 2022). There has been a long-standing focus on females in life-history research, and studies have only recently begun to consider male reproductive ageing (e.g., Fricke and Koppik, 2019; Comizzoli and Ottinger, 2021; Archer et al., 2022). Evidence suggests that male reproductive ageing can affect male fertilizing ability (Paul and Robaire, 2013; Aich et al., 2021), influence female behavior (Dean et al., 2010; Vuarin et al., 2019), and lead to paternal effects on offspring (Daxinger and Whitelaw, 2012). Male houbara bustards (*Chlamydotis undulata*), for example, produce fewer progeny as they age, and sons of old fathers have greatly reduced sperm numbers (Vuarin et al., 2019, 2021). Other studies show that male ageing can lead to lower sperm quality (Gasparini et al., 2010, 2014; Velando et al., 2011; Cornwallis et al., 2014; Selvaratnam and Robaire, 2016; Monaghan and Metcalfe, 2019; Vega-Trejo et al., 2019; Turnell and Reinhardt, 2020), and quantity (Johnson et al., 2015; Sepil et al., 2020). Additionally, sperm from older males have lower success in sperm competition and fertilize fewer eggs than sperm from younger males, as seen in guppies (*Poecilia reticulata*, Gasparini et al., 2019), zebra fish (*Danio rerio*, Kanuga et al., 2011) and crickets (*Acheta domesticus*, Reinhardt and Siva-Jothy, 2005). Sperm ageing can also affect the quality of offspring (Gasparini et al., 2017), characterized by offspring lifespan (Xie et al., 2018; Wylde et al., 2019), telomere length (Bouwhuis et al., 2018; Noguera et al., 2018; Bauch et al., 2019), development (Preston et al., 2015), reproduction (Bouwhuis et al., 2015; Vuarin et al., 2021), and viability (Tan et al., 2013). While most studies on male ageing have focused on sperm traits, only few have tested for changes in the quality and quantity of seminal fluid with age, and its resultant fitness outcomes. Therefore, whether the reported effects of male ageing are actually driven by changes in seminal fluid rather than just sperm are yet unknown.

Ejaculated sperm are usually surrounded by a cocktail of substances collectively called the seminal fluid (Poiani, 2006; Hopkins et al., 2017). These consist of somatic cells such as immune cells; macromolecules such as carbohydrates, vitamins, minerals; hormones; and seminal fluid proteins (SFPs). Seminal fluid (SF) in most species is made in specialized accessory reproductive cells, tissues, or glands, such as the prostate, seminal vesicle, bulbourethral, and ampullary glands in humans (McGraw et al., 2015). SFPs have been shown to be especially crucial in male and female reproduction; they belong to a range of molecular classes such as antioxidants, lipases, lectins, proteases, and protease inhibitors and have been shown to have a diverse set of functions (Chapman, 2001; Avila et al., 2011; Perry et al., 2013; Ramm, 2020). For instance, SFPs facilitate normal sperm function (Wolfner, 1997), aid sperm storage and male sperm competitiveness (Fiumera et al., 2005, 2007; Goenaga et al., 2015; Patlar et al., 2020), maintain sperm viability (den Boer et al., 2008, 2009; King et al., 2011) and regulate sperm capacitation (Manjunath and Thérien, 2002). But SFPs can also act on attributes beyond sperm, for example, by affecting female reproductive behavior (Chapman et al., 2003; Liu and Kubli, 2003; Bath et al., 2017). Indeed, seminal fluid has been shown to affect female immunity modulation (Short and Lazzaro, 2010), investment in the mating partner's male function in hermaphrodites (Nakadera et al., 2014), female egg-laying behavior (Chapman et al., 2003; Liu and Kubli, 2003), and mating plug formation to prevent female re-mating (Stockley et al., 2020).

The germline is predicted to receive higher protection from somatic ageing (Maklakov and Immler, 2016). Although seminal fluid is produced by somatic tissue it directly interacts with germ cells and thus could play an important role in facilitating interactions between somatic cells and the germline. This could have effects across the Weismann barrier (i.e., despite the germline and somatic tissue being separated early in development, changes in the soma could affect the germline or the next generation; Sciamanna et al., 2019; Bline et al., 2020). Knowing how seminal fluid changes with age and how this can influence sperm, offspring, and female physiological and behavioral responses to mating, in addition to understanding age-related changes in sperm, is essential to gain a complete picture of male reproductive ageing. Here, we first conduct a systematic review on how advancing male age influences the non-sperm components of the ejaculate (i.e., seminal fluid) across animals, and then discuss the impacts this might have on age-specific reproductive success. While the effects of male ageing on sperm have been reviewed elsewhere (e.g., Reinhardt, 2007; Pizzari et al., 2008; Monaghan and Metcalfe, 2019), to our knowledge, this is the first systematic review of how advancing male age affects seminal fluid. As studies differ greatly in their biological and methodological factors, which can modulate or confound male ageing effects, we discuss their possible influence on the conclusions that are reached.

2. Systematic review

2.1. Literature search and data collection

To understand how male age affects seminal fluid, we conducted a literature search following PRISMA eco-evo guidelines (O'Dea et al., 2021). We used a search string for abstracts, titles, and keywords "*(sfp* OR seminal fluid OR seminal plasma) AND (ageing OR age OR aging OR senescence)*" to identify studies which test how advancing male age affects seminal fluid, using two search engines: SCOPUS and Web of Science (WoS), on December 14th 2021, accessed through the University of Oxford server. The searches returned a total of 738 hits from WoS (year range: 1991 to 2021) and 620 from SCOPUS (year range: 1941 to 2021). After duplicate deletion, which was done using Rayyan (Ouzzani et al., 2016), we obtained a total of 970 unique papers. We then screened the abstracts of these papers using pre-defined inclusion and exclusion criteria (see below), before screening the full-texts to obtain a final list of papers from which relevant data was extracted.

To be retained for full-text screening, the paper had to be a research article (not review or meta-analysis), on any animal, and measure a seminal fluid trait for males of different ages, judged from its abstract. We excluded studies during abstract screening if they were on the wrong topic, did not compare males of different ages, did not have clear ageing data, only covered a small proportion of lifespan (e.g., only included young males), did not measure seminal fluid traits, or only measured seminal fluid during maturation of males (i.e., during juvenile or pubertal stages). The initial screening of abstracts produced a total of 94 studies whose full texts were considered in more detail.

When assessing full texts, to be included in our analysis review, a study needed to: compare males of non-overlapping age groups, compare non-sperm components of the seminal fluid (like oxidative stress enzymes, proteins, hormones, lipids, and macro- or micronutrients), report sample sizes of males in each age group and exact ages (or range of ages) to which males in each age group

belonged. We excluded studies whose full texts were not available (two studies), or which were not in English (three studies). We additionally conducted a scoping search on Google Scholar to obtain additional papers which might have been missed in our systematic screening and search. This was done by using the keywords "seminal fluid protein + aging + ageing + senescence" for each of the following taxa: "bulls," "insects," "pigs," "rodents," "humans," "birds," "mammals," "fish," and searching the first five search result pages for relevant studies.

From all studies which fulfilled our inclusion criteria, we collected information on how male age affected various non-sperm characteristics of the ejaculate, as described in the paper. Additionally, we collected data on factors which could modulate the influence of seminal fluid ageing, such as: male mating history (i.e., whether males were held as virgin or not prior to testing), at which ages males were sampled, what fraction of average lifespan was covered and sampling methodology. The fraction of average lifespan covered is likely to influence whether seminal fluid ageing is detected in a study because ageing trajectories are expected to follow a non-linear pattern, with senescence being more prominent in late-adult life (e.g., Jones et al., 2014; Lemaître et al., 2020b).

Male mating history could influence the ageing of seminal fluid, such that if males are kept virgins, old males would have stored seminal fluid for longer durations, thus have more degraded SFPs and higher accumulation of oxidative damage than mated old males or virgin young males. On the other hand, old virgin males would accumulate higher quantities of SFPs than younger virgin males (Koppik et al., 2018; Sepil et al., 2020). If previously mated males are tested the quantity of seminal fluid produced would depend on the timing of the last mating, number of times the male mated in succession and its rate of replenishment, given that the abundance of SFPs within accessory tissues/glands decreases significantly immediately after a mating event (Hopkins et al., 2019a; Sepil et al., 2019). Furthermore, if mating history is not controlled for, then older males would have mated more times over their life (e.g., Aich et al., 2021), and thus have undergone more rounds of SFP replenishment and thus potentially experienced a higher turnover of the glandular tissue producing the SFP than young males.

Male sampling methodology (if samples are collected longitudinally or cross-sectionally) can also have a large impact on the study outcome. Cross-sectional sampling of males makes age-dependent individual-level deterioration in ejaculate traits with advancing age harder to detect (Nussey et al., 2013), especially if low-quality males selectively disappear (Bouwhuis et al., 2009; Hämäläinen et al., 2014). This non-random age-dependent mortality could lead to biased sampling of males, where younger age classes would have higher variance and might bias estimates of averages in seminal fluid traits compared to old age classes. Thus, cross-sectional studies might underestimate male reproductive senescence, compared to longitudinal sampling measuring the same individuals at different ages.

2.2. Summary of studies from the systematic review

Overall, we obtained data from 27 papers through our systematic searches, and seven additional papers from Google Scholar (see Supplementary Table S1 for the full list of included studies). Out of these 34 studies, 14 reported how male age affected SFPs (see Table 1), although some of these studies reported changes in total protein content, while others, changes in specific SFPs only. 10 studies reported data on oxidative damage levels or anti-oxidants present in seminal fluid (henceforth collectively called "oxidative stress," see Table 2). Apart from these two components of the seminal fluid, a smaller fraction of studies assessed the concentration of lipids or lipoproteins (four studies), minerals/vitamins content (four studies), sugar content (two studies), or hormone concentrations (four studies) in the seminal plasma/ejaculate.

The low number of studies dedicated to male age-related changes in the seminal fluid is also reflected in the limited taxonomic breadth, with a strong focus on mammals (see Figure 1). Within mammals, studies were conducted on farm animals, humans, and laboratory rodents (see Supplementary Table S1). For most studies, males were sampled up to around 80% of their average adult lifespan and 50% of their maximum adult lifespan (see Tables 1 and 2 for lifespan sampled by studies; Supplementary Table S2 for sources of lifespan measurements). Another caveat is that non-significant results might go unpublished and it is difficult to estimate this extent, though a number of studies in our set of papers report no changes with age, so we hope the bias is not strong. In the following review, we restricted our discussion to studies that tested for male age-related changes in SFPs and oxidative stress response, as these aspects of the seminal fluid were better represented compared to other ejaculatory components.

2.2.1. Age-dependent changes in SFPs

Many studies that measured accessory tissue/gland protein content found an overall decline in SFPs with male ageing (Rezaei et al., 2015; Fraser et al., 2016; Koppik et al., 2018; see also Table 1). However, this pattern becomes less clear when considering studies that quantified individual SFPs or overall compositional changes. Here, some SFPs increased (Santhosh and Krishna, 2013; Simmons et al., 2014; Borziak et al., 2016; Inyawilert et al., 2019; Kant et al., 2019; Westfalewicz et al., 2021), while others decreased in abundance (Marshall et al., 2009; Rezaei et al., 2015; Koppik and Fricke, 2017; Herrera-Cruz et al., 2018; Ruhmann et al., 2018; Sepil et al., 2020; Westfalewicz et al., 2021) with male age. Furthermore, in studies which analyzed the full proteome of the seminal fluid only a small proportion of SFPs changed with age (e.g., Sepil et al., 2020).

Methodologies differed widely between studies, ranging from estimating changes in overall SFP content to reporting individual protein changes. Generally, studies which tended to report increases in SFPs with age (e.g., in *Homo sapiens*, *Bos taurus*, and *Teleogryllus oceanicus*) sampled <50% of the average lifespan of the species (e.g., Simmons et al., 2014; Kant et al., 2019; Westfalewicz et al., 2021). Hence, extending sampling to cover the entire average lifespan is crucial, especially when ageing trajectories are expected to follow a non-linear pattern, with senescence being more prominent in late-adult life.

Most studies on non-human mammals did not report male mating history (virgin or mated) prior to testing. In farm animal studies, older males are likely to have been mated as part of a breeding program, although this was not always explicitly stated. For studies on insects, males were primarily kept as virgins prior to testing. It is known that in *D. melanogaster*, age-related changes in SFPs depend on male mating history (Koppik and Fricke, 2017; Koppik et al., 2018; Sepil et al., 2020). Old unmated males transfer a lower abundance of SFPs in a first mating relative to young males, despite having a higher

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TABLE 1 Summary of studies testing the effect of male age on seminal fluid proteins across different taxa as found in the systematic search.

Study	Species	Proportion LS sampled	Sample sizes	Changes observed in SFPs	Sampling	Mating history
Borziak et al. (2016)	*Gallus gallus*	1 to 7 years out of 5.5 (avg in wild) and 18 (max)	16 total	Total of 1,141 SFPs identified, out of which nine changed with age*velocity, and four with age only. Protein tyrosine phosphatase type IVA 1 was present in old males only. Young males had more of SPARC precursor, acetyl-CoA acetyltransferase cytosolic, and ras-related protein Rab-11B compared to old males.	Cross-sectional	Mated but sexually rested
Inyawilert et al. (2019)	*Gallus gallus domesticus*	7 to 24 months out of 60 (avg) and 112 (max) months	18 total	Proteins with light (72 kDa) molecular weights decreased with increasing age. Mid-weight proteins (90 kDa) increased with increasing age. Heavy proteins (140 kDa) showed no significant change.	Cross-sectional	Unreported
Abou-Ahmed et al. (1993)	*Equus caballus*	7 to 25 years out of 25 (avg) and 47 (max) years	53 total	Total seminal fluid protein content was highest in middle aged males, and lowest in the youngest and oldest age groups.	Cross-sectional	Mated
Westfalewicz et al. (2021)	*Bos taurus*	2 to 4 years out of 10 (avg) and 25 (max)	6 total	17 SFPs differed between young and old males. Older bulls had higher abundances of: glutathione; S-transferase omega 2 (GSTO2); PRDX5; PARK7; superoxide dismutase (SODC), compared to younger males. Younger bulls had higher amounts of: keratin, type II cytoskeletal 59 kDa, component IV (K2C4); outer dense fiber protein 2 (ODF2); tektin-5 (TEKT5) and TBB2B compared to older bulls.	Longitudinal	Unreported
Fraser et al. (2016)	*Sus scrofa*	19 to 42 months out of 66 (avg) and 264 (max) months	4 total	Overall content of seminal fluid proteins declined with age. Did not identify specific SFPs.	Longitudinal	Unreported
Kant et al. (2019)	*Homo spaiens*	20 to 40 years out of 72 (avg) and 120 (max) years	6 per age group	17 protein spots and 10 proteins differed between young and old groups (humans are known to contain ~3,000 SFPs). Glutaredoxin domain containing cysteine-rich protein-2, clusterin, serum albumin, translation initiation factor IF-2 like, ecto-ADP-ribosyltransferase 4, CB1 cannabinoid receptor-interacting protein 1, serotransferrin were found in higher abundance in older males compared to younger males. Alternative protein RRT-34 and protein Unc-119 homolog A were found in lower abundance in older age samples compared younger males.	Cross-sectional	Mated
Simmons et al. (2014)	*Teleogryllus oceanicus*	4 to 20 days out of 74 (avg) and 135 (max) days	57 total	Total of 27 distinct SFPs identified. Total protein content did not vary with age. ToSfp014, ToSfp025, ToSfp007 (Trypsin-like serine protease), ToSfp017, ToSfp011, ToSfp026, ToSfp005 (Dipeptidase), ToSfp027 (apyrase), ToSfp001, ToSfp024 (carbonic anhydrase) increased with age. Other SFPs did not change significantly with age.	Cross-sectional	Virgins

(Continued)

TABLE 1 (Continued)

Study	Species	Proportion LS sampled	Sample sizes	Changes observed in SFPs	Sampling	Mating history
Koppik and Fricke (2017)	*Drosophila melanogaster*	7 to 42 days out of 45 (avg) and 110 (max) days	10 per age group	All five SFP genes tested decreased in expression with age: Acp26Aa, Acp29AB, Acp36DE, SP and Acp62F.	Cross-sectional	Mated and unmated treatments
Sepil et al. (2020)	*D. melanogaster*	7 to 35 days out of 45 (avg) and 110 (max) days	80 per age group	117 SFPs identified, out of which 40 changed with age. Focused on six functionally important SFPs. Acp62F, Semp1, and Acp26Aa decreased with age. Acp70A [sex peptide], Acp36DE, and CG9997 showed no change with age. Age-related accumulation of SFPs in unmated males, but reduced transfer. No change in SFP abundance or transfer with age in frequently-mating males. Evidence of age related post-translational modifications in some SFPs.	Cross-sectional	Mated and unmated treatments
Rezaei et al. (2015)	*D. melanogaster*	2 to 53 days out of 45 (avg) and 110 (max) days	20 per age group	Overall seminal fluid amount decreased with age. Did not measure specific SFPs.	Cross-sectional	Virgins
Ruhmann et al. (2018)	*D. melanogaster*	4 to 42 days out of 45 (avg) and 110 (max) days	18 per age group	Measured two SFPs: sex peptide and ovulin. Sex peptide decreased in old males, ovulin levels did not change with age.	Cross-sectional	Mated
Herrera-Cruz et al. (2018)	*Anastrepha ludens*	8 d to 72 days out of 50 days (avg), 1 year (max)	20 per age group	Old males had lower overall protein content in their testis (but not accessory glands) compared to young males.	Cross-sectional	Virgins
Marshall et al. (2009)	*Allonemobius socius*	5 to 40 days out of 35 days (avg) and 100 days (max)	42 total	Protein X (trypsin like serine protein) reduced with male age.	Cross-sectional	Virgins
Santhosh and Krishna (2013)	*Drosophila bipectinata*	2 to 47 days out of 58 days (avg) and 200 days (max)	50 per age group	Overall SFP quantity increased with male age.	Cross-sectional	Virgins

Proportion lifespan (LS) sampled is given in relation to reported average lifespan (avg) or maximum (max) recorded lifespan (sources for those numbers can be found in Supplementary Table S2) for each species.

abundance of SFPs in storage, whereas old frequently mated males show no change in either transfer or storage (Sepil et al., 2020). Thus, mating history has the potential to influence the results reported in studies which do not control for it. We suggest future studies should adopt a fully factorial design to test for effects of mating history on seminal fluid ageing and use young and old males both as virgin and mated males, and ideally control for mating number.

In most studies, samples were acquired from the male directly (e.g., *via* dissection or masturbation), but whether this correctly represents what would be transferred to females in a natural ejaculate is uncertain, especially when males have the potential for strategic ejaculation (Wedell et al., 2002). Moreover, the vast majority of studies were cross-sectional. It would be ideal to conduct longitudinal studies in species where males do not need to be sacrificed to extract their ejaculate and a large cohort of males can be followed across their lifetime.

2.2.2. Age-dependent changes in oxidative stress responses

Overall, the enzymes involved in protecting against oxidative damage decreased significantly in the seminal fluid with advancing male age (see Table 2). The three studies that measured both enzyme abundance and oxidative stress in the seminal fluid found oxidative stress markers increased in older males. Specifically, all studies which measured antioxidant content in the seminal fluid (e.g., TSOD, MnSOD, CuZnSOD, TGSH, CAT) consistently reported a decline in older males compared to younger or middle-aged males. Additionally, an oxidative stress marker was found in higher quantities in older male seminal fluid compared to younger males in two studies (El-Gindy and Zeweil, 2017; Kara et al., 2019). Notably, all these oxidative stress studies used mammals, so we cannot judge whether this is a pattern also seen in other animal groups. None of these studies reported the mating history of the males, and only one study sampled males longitudinally (Fraser et al., 2016).

3. Discussion

Here, we systematically reviewed how the non-sperm components of the ejaculate (i.e., seminal fluid) changed with male age. Sperm ageing has been a major focus of previous studies, while seminal fluid has not been studied as extensively. This is highlighted

TABLE 2 Summary of studies found in the systematic literature search that focus on male-age dependent changes in antioxidants, oxidative stress biomarkers and reactive oxygen species in male ejaculates/seminal plasma.

Study	Species	Proportion LS sampled	Sample sizes	Changes observed in oxidative stress	Sampling	Mating history
Vince et al. (2018)	*Bos taurus*	2 to 10 years out of 10 (avg) and 25 (max)	9 young, 9 old	Antioxidants such as TSOD, MnSOD, CuZnSOD, TGSH, CAT all higher in young males. Oxidative stress was higher in old males.	Cross-sectional	Unreported
Ahmad et al. (2020)	*Bos taurus*	3 to 10 years out of 10 (avg) and 25 (max)	6 young, 6 old	Younger bulls had higher total antioxidants. For catalase and malondialdehyde, there was no sig. difference.	Cross-sectional	Unreported
Majić Balić et al. (2012)	*Bos taurus*	2 to 10 years out of 10 (avg) and 25 (max)	9 young, 10 old	Season dependent changes in antioxidants: For total glutathione peroxidase (T-GSH-Px), young bulls had more in all seasons. For glutathione peroxidase (Se-GSH-Px), protein carbonyl content (PCC), young males had more in 3/4 seasons.	Cross-sectional	Unreported
Kelso et al. (1997)	*Bos taurus*	2 to 9 years out of 10 (avg) and 25 (max)	4 in each of the three classes	For both antioxidants measured, glutathione peroxidase and superoxide dismutase, younger males had more than older males.	Cross-sectional	Unreported
Noguera et al. (2012)	*Gallus gallus*	1 to 4 years out of 5.5 (avg in wild) and 18 (max)	6 young, 15 old	Decrease in antioxidants such as -SH group of proteins, uric acid, vitA, vit C, vit E in old males.	Cross-sectional	Unreported
El-Gindy and Zeweil (2017)	*Oryctolagus cuniculus*	9 to 42 months out of 24 months (avg) and 150 months (max)	18 young, 18 old	Aspartate transaminase showed no significant change with age. Antioxidants decreased in old males. Oxidative stress marker malondialdehyde increased sig in old males.	Cross-sectional	Unreported
Kara et al. (2019)	*Mus musculus*	3 to 24 months out of 24 (avg) and 48 (max) months	14 young, 21 old	Antioxidants glutathione peroxidase and reductive glutathione decreased in older males. Oxidative stress marker malondialdehyde increased in old males.	Cross-sectional	Unreported
Fraser et al. (2016)	*Sus scrofa*	19 to 42 months out of 66 (avg) and 264 (max) months	4 in total	Antiperoxidant activity lower in older animals. Antioxidant L-glutathione concentration peaked at mid age 19–30 mo, and declined in older animals.	Longitudinal	Unreported
Waheed et al. (2013)	*Equus caballus*	4 to 22 years out of 25 (avg) and 47 (max) years	6 in each age group	Antioxidant glutathione peroxidase highest in middle aged males, and lower in oldest and youngest males.	Cross-sectional	Unreported
Takemura et al. (2014)	*Rattus norvegicus*	15 to 75 weeks out of 124 (avg) and 187 (max) weeks	4 to 5 in each group	DJ-1 antioxidant decreased with age. Cu/ZnSOD antioxidant decreased with age.	Cross-sectional	Unreported

Proportion lifespan (LS) sampled is given in relation to reported average lifespan (avg) or maximum (max) recorded lifespan (sources for those numbers can be found in Supplementary Table S2) for each species.

by the limited number of studies and taxa found in our systematic review, with the majority of studies either probing at age-related changes in SFPs or oxidative stress. Below, we discuss how the age-dependent changes in seminal fluid components found in our systematic review might influence male reproductive ageing, suggest some hypotheses, and discuss why the omission of seminal fluid and its associated somatic tissue is an important oversight in evolutionary and ecological research.

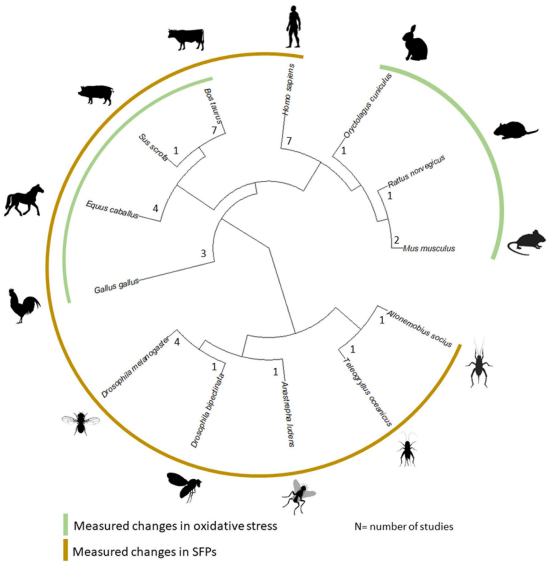

FIGURE 1
Phylogenetic distribution of all species in our review across 34 studies along with the number of studies on each. Species which had data reported for age-dependent changes in SFPs and oxidative stress are marked. Images to generate the figure were taken from the Open Tree of Life.

3.1. Seminal fluid protein ageing

We found some heterogeneity between studies in age-related SFP changes. This could be due to studies reporting quantitative changes in a set of proteins only (rather than all the proteins), or due to specific proteins responding differently to age based on their function or tissue-of-origin (Borziak et al., 2016; Sepil et al., 2020). Proteomics techniques that quantify the whole ejaculate are needed to better elucidate these biological patterns and with the advance of molecular approaches and particularly proteomics, this will become ever more feasible for a range of taxa.

Confounding factors could also explain some of the inconsistencies observed between studies. For instance, male mating history could have a large influence on SFP quantity changes as explained in the methods section above. Another caveat in comparing studies is that males are not always sampled up to old age and so an important fraction of the ageing trajectory is missed. This could be a serious bias, potentially compounded by there being stronger selection to maintain functionality earlier in life, meaning realised phenotypes may in part represent compensatory adaptive responses to the onset of seminal fluid ageing. Disentangling age-related changes from compensatory responses would require sampling beyond the 50% average lifespan into older ages, when the latter responses are expected to wane as the strength of selection declines.

While studies in our review rarely directly discuss the functional importance of the changes in observed SFPs, below, we suggest testable hypotheses for how male seminal fluid ageing might have functional consequences. Overall, studies in our review show changes in specific SFP abundances which are known to influence male fertilization success as well as a variety of female responses. For instance, older male *D. melanogaster* are less able to delay female remating and stimulate egg laying compared to younger males (Koppik and Fricke, 2017; Ruhmann et al., 2018; Sepil et al., 2020). Similarly in *Aedes aegypti* mosquitoes, older males are less able to prevent female remating (Agudelo et al., 2021). These responses are largely mediated by SFPs in *D. melanogaster* (Chapman et al., 2003) and the expression of functionally important SFPs declines with age (Koppik and Fricke, 2017). Therefore, it is possible that the decline in SFPs are driving the changes in female post-mating behavior. For instance, Sepil et al. (2020) found a significant age-related increase in SFP abundances in the accessory glands of unmated males, but no change in SFP abundances in the accessory glands of frequently-mated males. Yet, the authors also found that female egg laying behavior and remating affinity changed as a function of male age following matings with spermless males, hence the seminal fluid alone does contribute to the decline in reproductive function with male age. SFP transfer data can partially explain these findings. While there is no age-related decline in SFP abundances in the accessory glands, old unmated males transferred a lower quantity of SFPs to females compared to younger unmated males. There was no age-related change in the quantity of SFPs transferred to females for frequently-mated males, so it is likely that changes in SFP quality rather than quantity explain the decline in reproductive function with age in this group of males.

Apart from affecting male ability to induce female post-mating responses, age-related changes in seminal fluid might also affect sperm traits. For example, in the jungle fowl *Gallus gallus*, age-related changes in proteins which affect sperm velocity were detected (Borziak et al., 2016). Thus, the decreased ability of older males to gain paternity under sperm competition and fertilize eggs may be driven by changes in SFPs rather than changes in sperm *per se*.

While it can be difficult to pinpoint the precise changes responsible, it is becoming increasingly possible to manipulate the expression of individual SFPs to better understand how particular SFPs affect female post-mating behavior and sperm competition. For instance, using a combination of proteomics and RNAi, Marshall et al. (2009) identified a single accessory gland-derived ejaculate protein in the ground cricket *Allonemobius socius* that influences female egg-laying and declines in expression with male age. Hence, this protein is a prime candidate to explain the waning ability of males to induce female egg laying as the male ages. However, the link between seminal fluid expression and female responses is not necessarily straightforward. RNAi knockdown studies in other taxa have demonstrated that suppressing the expression of individual SFPs can have both positive and negative impacts on fitness-relevant traits such as female fecundity (Xu et al., 2013; Weber et al., 2019), though this may in part reflect the difficulty of measuring fitness components under realistic conditions. A further limitation of many such knockdown or knockout studies is that they tend (often of necessity) to consider only one or a few seminal fluid proteins, whereas in reality the seminal fluid proteome is a highly integrated unit whose individual components co-vary in their expression (Mohorianu et al., 2018; Patlar et al., 2019).

3.2. Effects of male age on seminal fluid quantity versus quality

In addition to changes in the abundance of individual proteins or changes to the composition of the seminal proteome, ageing can

potentially impact seminal fluid through alterations to protein quality. A loss of protein homeostasis – proteostasis – is a well-known feature of ageing, characterized by a failure of chaperones, stress-response factors, and protein degradation machinery to respond to stress and prevent protein misfolding (Labbadia and Morimoto, 2014). The role of failing proteostasis in loss of SFP quality in ageing males is currently unclear but has the potential to impact ejaculate function.

Work in *D. melanogaster* suggests that factors other than SFP *quantity* may be responsible for the decline in seminal fluid-mediated functions with male age (Sepil et al., 2020). Aged males, that are known to have compromised fertility and reduced seminal fluid function, still appear capable of levels of seminal proteome production and transfer that are similar to young males (Sepil et al., 2020). However, several proteins in aged males show evidence of qualitative changes *via* mass shifts on Western blots (Sepil et al., 2020). While it remains to be investigated how widespread age-related changes in SFP quality are and what the functional consequences are, it nonetheless raises the possibility that a decline in SFP functionality with age is primarily related to proteostasis loss, rather than diminishing amounts of SFPs.

3.3. Ageing of seminal fluid producing reproductive tissues

While our systematic review showed general age-related declines in SFPs, how the somatic tissues which produce SFPs are affected by ageing across taxa still remains unclear. Generally, the size of prostates/accessory glands tends to increase as males grow older (Jin et al., 1996; Atalan et al., 1999; Rezaei et al., 2015; Reyes-Hernández and Pérez-Staples, 2017), but shrinkage with age was also reported in few studies (Mazeed and Mohanny, 2010; Santhosh and Krishna, 2013). However, the overall size of the organ does not necessarily predict protein content, as found in *A. ludens* (Herrera-Cruz et al., 2018) and *D. bipectinata* (Santhosh and Krishna, 2013). In humans, the increase in prostate size is known as benign prostatic hyperplasia (Berges and Oelke, 2011; Zhang et al., 2013), however prostate size varies among ethnic groups and so does the rate of change with age (i.e., Bolivian Tsimane, Trumble et al., 2015) or the occurrence of enlarged prostates in older males (Mubenga et al., 2020). Some theory predicts that the enlargement of the prostate is a side-effect of cellular hyperfunction that causes ageing of this tissue (Blagosklonny, 2021). The hyperfunction theory of ageing proposes that suboptimal nutrient-sensing molecular signaling in late-life causes ageing *via* excessive biosynthesis, as opposed to energy-tradeoffs (Lind et al., 2019).

3.4. Impact of male age on oxidative stress

The studies we reviewed consistently found that antioxidant quantity in the seminal fluid decreases with increasing male age, while oxidative stress markers tend to increase in the seminal fluid as males age. Reactive oxygen species (ROS) are unstable, free radical compounds and are required for vital cellular processes (Finkel and Holbrook, 2000; Hajam et al., 2022), but can also be deleterious to cells. For instance ROS play a role in sperm activation and changing sperm motility, e.g., in humans (Aitken et al., 2022) with the potential to influence male reproduction (Mannucci et al., 2022). However, work in *D. melanogaster* shows that while older males have higher metabolic rates in their sperm, ROS production is actually lower in these sperm (Turnell and Reinhardt, 2020).

Antioxidants, on the other hand, play a key role in stabilizing free radicals generated as part of cellular processes (Hood et al., 2019), and an imbalance between antioxidants and ROS causes oxidative stress. Oxidative stress has been shown to influence sperm homeostasis and can cause sperm DNA damage thus affecting male fertility (Mannucci et al., 2022) and has been shown to be key in regulating various intracellular pathways related to sperm, and activation of various sperm transcription factors (Aitken and Baker, 2006; Sabeti et al., 2016; Aitken, 2017). Our review suggests that older males have lower antioxidant levels but higher oxidative stress markers in their seminal fluid, and thus may have higher oxidative stress than young males. The decline in antioxidants might indicate a tradeoff where ageing males cannot maintain optimal antioxidant levels if these are energetically costly.

The mechanisms for why older males have higher oxidative stress could be several. For instance, ROS from sperm could "leak" into seminal fluid or somatic cells which produce SF could accumulate more ROS damage over time in old versus young males. This increase in oxidative stress in older males could have severe hypothesized functional consequences, such as higher oxidative damage to sperm, or the fertilized egg, and reduced sperm performance, which can be tested by future studies. More studies are needed to disentangle the origin/cause of age-dependent changes in ROS production in seminal fluid, the consequences of scavenging by SF antioxidants, and the overall effects on sperm, male and female reproduction.

3.5. Factors that could influence seminal fluid ageing rates

Studies identified in our systematic literature review included only a few factors such as proportional lifespan sampled, male mating history and sampling of males to explain differences in seminal fluid ageing.

Besides these, other factors could be predicted to influence SF ageing. For instance, evidence for reproductive ageing has been shown to be stronger in laboratory and captive animals compared to wild ones (Nussey et al., 2013; Zajitschek et al., 2020; Kappeler et al., 2022). Additionally, domestic animals, which were used in a majority of studies found in our systematic review, are kept in semi-controlled conditions and are killed off prior to reaching a senescent age (i.e., post their "prime"). Thus, evidence for reproductive senescence in the seminal fluid may be weaker in domestic animals, although in our review, we found evidence for seminal fluid senescence in both lab and domestic animals.

Other abiotic and biotic factors could influence seminal fluid ageing, such as a male's social environment. Both sperm and seminal fluid are highly plastic in their expression (reviewed in Perry et al., 2013; and Ramm, 2020). Males are known to invest more in seminal fluid production under more competitive environments, such as under high sperm competition (Hopkins et al., 2019b), possibly at the cost of reduced later-life investment in reproduction (Lemaître et al., 2020a). The costs of ejaculate plasticity have been discussed before (see, e.g., Ramm, 2020), but to our knowledge have not been tested, and whether these costs differ for old versus young males can

be investigated in the future. Knowledge of costs could be one factor predicting ageing trajectories of seminal fluid. If seminal fluid production is costly and its continued production causes damage, then strong selection on early reproduction might be favoured and we would expect rapid ageing as a consequence. However, if seminal fluid production is cheap then factors such a sperm competition, male dominance and/ or female preferences might have more scope to shape ageing patterns. For example if old males are socially dominant and preferred by females they might face little competition and selection on seminal fluid is relaxed and thus ageing might arise. Conversely, if older males are more likely to experience sperm competition or female ejaculate rejection then there might be relatively high selection for seminal fluid competency late in life. Additionally, sperm production patterns, i.e., continuously versus one bout early in life, and whether sperm is the limiting factor might be important too, because supply and demand needs to be balanced between these different components through reproductive lifespan. To test these ideas knowledge of ejaculate ageing across a broad range of taxa with different reproductive patterns is necessary.

Mating systems can also influence ageing of seminal fluid. Ageing effects are expected to be more pronounced in polyandrous species where males are likely to invest more in their ejaculates (Veltsos et al., 2022), due to facing a higher risk of sperm competition. However, the influence of sperm competition on male reproductive senescence likely depends on the life-history of a species. For example, in some species, males may preferentially invest resources in producing more SFPs early in life, and suffer faster rates of reproductive senescence later in life (see also Lemaître et al., 2020a). Older males in such species are often inferior in both pre- and postcopulatory competition (Johnson and Gemmell, 2012; Gasparini et al., 2019) and are discriminated against by females (Velando et al., 2011; Rezaei et al., 2015). Alternatively, species with increased levels of sperm competition may evolve increased investment in SF (Immler et al., 2011; Lüpold et al., 2020), which may reduce the rate of senescence in these ejaculate traits (Delbarco-Trillo et al., 2018).

Abiotic factors such as nutrition could also impact the trajectory of ageing of the seminal fluid. Studies on male rats showed that both over- and undernutrition during pregnancy seem to lead to premature male reproductive ageing (reviewed in Zambrano et al., 2021). This is because, at least in mammals, the early stages of development have an overall impact on health and quality of life during adulthood (developmental programming) with endocrine disruptors and maternal nutrition impacting developmental programming.

3.6. Male ageing effects on offspring fitness *via* seminal fluid

The impact of male age is not limited to his own and his mates' reproductive success, but potentially extends to offspring fitness as well. Males are known to influence the fitness of their offspring through mechanisms other than the transmission of DNA (Curley et al., 2011; Crean and Bonduriansky, 2014). Advanced paternal age has been shown to shorten offspring lifespan, exacerbate ageing-related pathology and to alter offspring social behavior (Kong et al., 2012; Brenman-Suttner et al., 2018; Xie et al., 2018). Classically, these impacts were believed to be due to the accumulation of *de novo* mutations in ageing germ cells. However, recent work suggests that non-genetic mechanisms, such as changes in methylation patterns or small non-coding RNA populations, are more likely to drive the intergenerational effects of ageing (Xie et al., 2018). Importantly, it was recently suggested that seminal fluid might be an under-appreciated mediator of paternal effects (Simmons, 2011; Watkins et al., 2018; Evans et al., 2019; Simmons and Lovegrove, 2019, 2020; Kekäläinen et al., 2020), yet this has not yet been tested in a paternal ageing context.

4. Conclusion

Despite the low number of studies found, our review is crucial in highlighting the gaps in our knowledge of seminal fluid ageing. Our review generates hypotheses on how ageing of seminal fluid could affect male and female fitness, and makes predictions for how various biological and methodological factors could modulate the effects of seminal fluid ageing. It further shows that ageing impacts the level of oxidative stress in the seminal fluid, and to some extent the abundance of SFPs in the ejaculate. We highlight how the age-dependent changes observed in the seminal fluid profile can affect male fitness. Additionally, we find that male ageing can alter expression or abundance of specific SFPs that regulate female post-mating behavior (Koppik and Fricke, 2017; Sepil et al., 2020), oviposition rate (Marshall et al., 2009), male sperm competition (Ruhmann et al., 2018; Sepil et al., 2020), response to oxidative stress (Kant et al., 2019; Westfalewicz et al., 2021), immune and antimicrobial function (Borziak et al., 2016), and sperm velocity (Borziak et al., 2016). Most research to date has been done on mammals and insects, specifically on species important for animal husbandry or biomedicine. Hence, broadening the taxonomic spread of future studies in general, and the inclusion of species with different mating systems in particular should be a priority.

We highlight how understanding reproductive ageing of sperm, but also of the seminal fluid and the tissues producing them can provide a better picture of male reproductive ageing. Any future research agenda must therefore include a more focused assessment of the downstream consequences of seminal fluid ageing on fitness-related traits, encompassing impacts on fertility, sperm competitive ability and effects on the resulting offspring. Future work should ideally study the non-sperm ejaculate components as a whole, together with changes in sperm as this will be key to advance our understanding of male reproductive ageing.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

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