Genetics of 44 female and male reproductive traits and their relationship with health, longevity and consequences for offspring

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Abstract

Substantial shifts in reproductive behaviors have recently taken place in many high-income countries including earlier age at menarche, advanced age at childbearing, rising childlessness and a lower number of children. As reproduction shifts to later ages, genetic factors may become increasingly important. Although monogenic genetic effects are known, the genetics underlying human reproductive traits are complex, with both causal effects and statistical bias often confounded by socioeconomic factors. Here, we review Genome–Wide Association Studies (GWAS) of 44 reproductive traits of both female and male individuals from 2007–early 2024, examining reproductive behavior, reproductive lifespan and aging, infertility and hormonal concentration. Using the GWAS Catalog as a basis, from 159 relevant studies we isolate 37 genes that harbor association signals for four or more reproductive traits, more than half of which are linked to rare Mendelian disorders, including 10 genes linked to reproductive-related disorders: *FSHB*, *MCM8*, *DNAH2*, *WNT4*, *ESR1*, *IGSF1*, *THRB*, *BRWD1*, *CYP19A1* and *PTPRF*. We also review the relationship of reproductive genetics to related health and behavioral traits, aging and longevity and the impact of parental age on offspring outcomes, as well as reflecting on limitations, open questions and challenges in this fast-moving field.

Key words: reproductive aging; reproductive lifespan; fertility; infertility; GWAS; genetics

Main

Human reproduction involves a wide range of biological, genetic and socioeconomic factors (see **Box 1** for definitions).[1] Substantial reproductive shifts have taken place in the last decades in many high-income countries, including earlier ages at menarche[2] and sexual debut,[3] postponement of childbearing, lower number of children and rising childlessness (**Fig. 1**).[4,5] In many Western European and East Asian countries, first births are now taking place at age 30 and higher (**Fig. 1**). This means that people are having children at ages when their fecundity (ability to conceive) starts to wane.[6] Parents are also having longer birth intervals between children,[7] with an increase in later births after the age of 40.[8]

Insert Figure 1: Total female fertility rate and change in mean age at first birth.

At the same time, the prevalence of lifetime infertility is estimated at 17.5%,[9] with 1 in 6 couples facing infertility issues. There is also an increase in childlessness, which includes both involuntary infertile individuals and voluntary 'childfree' individuals, choosing not to have children. In fact, 20% of women born in 1965 who reached the end of their reproductive lifespan remain childless, which is even higher in East Asian countries such as Japan, where 28% of women born in 1975 remained childless.[4] For Finnish men, for instance, levels of lifetime childlessness by age 40 (born 1969-1971) are one-third of the population.[10] Multiple factors have been attributed to these shifts, including effective contraception, availability of legal abortions, inability to find a partner, women's entry into higher education and employment, economic uncertainty, health, changing preferences, gender norms alongside work-life reconciliation structural factors such as availability of childcare and flexible work (see **Box 2** for how we define and use terms related to sex and gender).[1]

The socio-cultural context in turn interacts with genetic influences on fertility, as norms and institutional structures that enable or constrain reproduction change over time.[11] As childbearing and the reproductive lifespan shifts to later ages, genetic factors which were hitherto not observed may become increasingly important. Almost 50% of infertile cases are attributed to a genetic defect, with considerable research on monogenic causes (see **Box 3**).[12] SNP-heritability estimates, which measures the proportion of single nucleotide polymorphism variance or the upper ceiling we might expect of genetic effects in GWASs of SNP arrays, demonstrate that genetics plays an important role in reproduction. Estimates across traits include age at first birth (0.15, SE 0.04),[13] age at menarche (0.32, SE 0.01),[14] age at menopause (0.06, SE 0.02),[15,16] number of children ever born (0.10, SE 0.05),[13] endometriosis (0.26, SE 0.04),[17] and uterine fibroids (0.33, SE 0.18).[18] Twin studies estimate higher levels of heritability ranging between 0.10 to 0.43 for example for age at first birth and number of children.[19]

Insert Box 1: Glossary of selected reproductive terms

The aim of this review is to synthesize findings of the genetics of reproductive traits and behavior from 2007–early 2024. We leverage Genome Wide Association Studies (GWAS)

registered in the GWAS Catalog,[20] which have discovered multiple common genetic variants related to reproductive traits, including reproductive behavior, reproductive lifespan, infertility and related hormonal concentration. We summarize these findings, and describe links to other related behavioral and health traits and longevity and the genetic consequences of parental age on offspring. Finally, we conclude by outlining challenges, gaps in research and future directions.

Reproductive traits and reproductive aging

Reproductive traits

Reproductive traits refer to traits associated with reproductive lifespan and aging (age at menarche or voice breaking, age at natural menopause), reproductive behavior (age at first sex, age at first birth, number of children ever born), infertility or those affecting lifespan or health outcomes (endometriosis, uterine fibroids and related, polycystic ovary syndrome (PCOS), recurrent pregnancy loss, sperm-related, sexual dysfunction) and related hormonal concentration (gonadotrophins follicle-stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, anti-Müllerian hormone (AMH), testosterone). Within this, there are key terms and variation in focus across areas of expertise in reproductive medicine, genetics and demography (see **Box 1**). The genetic architecture of reproductive traits and aging includes monogenic causes of rare variants with large effect sizes to hundreds of low frequency and common variants associated with these traits, often combined into polygenic scores.[15] We focus on the range of these genetic associations and note extensive research in the area of monogenic and Mendelian genetic disorders related to infertility, largely outside the scope of our review (see **Box 3**).

Reproductive aging

The majority of research examines the reproductive lifespan from fecundity, defined as the initial signs of puberty generally occurring between the ages 8–13 years,[21] up to the age of menopause (40-55) [22] and often to completion of childbearing at around 55 for the majority of male individuals.[23] There are some exceptions, such as the 0.5% of female individuals who have primary ovarian insufficiency (POI), resulting in early menopause before the age of 40.[24] Reproductive aging is a multifactorial and multi-stage process that can be partitioned into four phases of reproductive initiation, peak reproduction, reproductive decline and post-reproduction (**Fig 2.**). Oocytes produced during fetal development steadily decline throughout life until menopause. In females, reproductive decline is marked by age at natural menopause.[25] In males, reproductive aging has been associated with lower testosterone levels,[26] decrease in the number of Sertoli cells[27] and semen parameters (e.g., ejaculate volume, sperm concentration,

sperm motility) which start to decline at 34-35 years of age.[28] The genetics of reproduction cannot be examined in isolation since related health factors and tsocio-environmental context interact with reproductive behavior and genetically-related reproductive traits and aging. For example, parental monitoring, socioeconomic status or genetically-related phenotypes of externalizing behavior such as self-control or risk-tasking have been associated with earlier sexual debut and pregnancy.[3]

Insert Figure 2: Timeline of reproductive aging

The genetics of reproductive traits and aging

Scope, search strategy and study selection

Previous findings have isolated a variety of monogenic and rare genetic factors that contribute to infertility (see **Box 3**). Since 2005, understanding the genetics of reproductive traits and aging are largely driven by GWAS discoveries. A GWAS regresses a reproductive trait on each measured SNP (i.e., genetic variant where the DNA – A,C,T,G allele – varies at a genomic location across the population) across the genome.[29] Given multiple testing, a *p*-value threshold based on Bonferroni correction of 5×10^{-8} is used to signify an association between a common genetic variant and a trait, which we also adopt in this study.

Most GWASs are registered in the GWAS Catalog,[20] which we draw from up to May 2024 on broad search terms: "AMH", "FSH", "LH", "PCOS", "SHBG", "age at first birth", "age at first live birth", "age at first sex", "age at last birth", "age at last live birth", "age at voice", "anti müllerian", "anti-müllerian", "erectile", "estradiol", "fertility", "gestational", "gonadotrophins follical", "hysterectomy", "luteinizing hormone", "menarche", "menopause", "menstrual", "miscarriage", "number of children", "number of sexual partners", "oestradiol", "ovarian", "ovaries", "ovary", "pelvic", "physiological sexual disorder", "preeclampsia", "pregnancies", "pregnancy", "pubertal", "puberty", "reproductive", "sex hormone binding globulin", "sex hormone-binding globulin", "sexual dysfunction", "sperm", "testicle", "testicular", "testis", "testosterone", "twinning", "twins", "uterine", "uterus". Given the variability in registering terms, we supplemented our keyword search with a further manual search.

We isolated 194 studies and after excluding unrelated work (e.g., brain imaging traits), we were left with 159 studies and 44 traits (Supplementary Table 1). Many of these traits had multiple naming variations in the “Reported trait” column in GWAS catalog. Supplementary Table 2 illustrates how these term variations were mapped to the 44 traits.

Insert Box 3: Monogenic and rare reproductive disorders

Genome-wide associations

In 2009, GWASs on age at menarche,[30–33] menopause,[34] testicular cancer[35,36] and ovarian cancer[37] were published. Since then, over 100 GWASs have investigated the contribution of genetics to reproductive phenotypes such as age at voice drop in boys,[38] age at first birth,[3,39] endometriosis,[40,41] testosterone levels,[42,43] number of children ever born[3,39] and miscarriage.[44] This effort has yielded thousands of genotype-phenotype associations and shown that multiple SNPs over the genome contribute to reproduction. These associations can be mapped to hundreds of genes, many of which harbor associations with multiple reproductive phenotypes (**Table 1**). Given that many reproductive traits are highly correlated, such as sex hormone binding globulin (SHBG) and testosterone,[42] this is not unexpected. Notably, some of these genes (*LINC01505, LIN28B-AS1, MCHR2, IGSF1*) are implicated in both male-specific and female-specific reproductive traits **(Fig. 3, Table 1).**

Insert Table 1. Top GWAS reproductive trait genes.

Due to linkage disequilibrium (LD) and other factors, it is sometimes difficult to ascertain the causal genes and variants within the genomic loci that have associations from GWAS. There is also considerable overlap and correlations of the genes identified for reproductive traits. The GWAS catalog maps genetic variants to genes with an automated Ensembl pipeline that delivers any Ensembl genes that the SNP in question maps to or the nearest upstream and downstream gene within 50 KB. [20] Looking at those mapped genes for reported associations with P<5E-8 in the GWAS catalog for the range of phenotypes found in Supplementary Table 2, we isolated 37 genes/gene-loci that harbor association signals for four or more different reproductive traits (Supplementary Table 3). More than half of those genes have previously been linked to rare Mendelian disorders according to OMIM (Online Mendelian Inheritance in Man, www.omim.org), an online resource that contains information about approximately 16,000 genes and all Mendelian genetic disorders.[45] Of those, 10 genes in total have been linked to reproductive related Mendelian disorders: *FSHB, MCM8, DNAH2, WNT4, ESR1, IGSF1, THRB, BRWD1, CYP19A1* and *PTPRF* (**Table 1**).

Insert Fig. 3 | Genetically-regulated reproductive traits.

FSHB (follicle stimulating hormone subunit beta) overlaps with RNA gene *ARL14EP-DT*, which is the top reproductive trait gene that appears across the most reproductive traits, harboring GWAS signals for eleven different reproductive phenotypes (**Table 1**). *FSBH* is part of the pituitary glycoprotein hormone family, which includes follicle stimulating hormone (FSH), luteinizing hormone (LH), chorionic gonadotropin and thyroid-stimulating hormone and twinning frequency.[46] Hormones previously found to play a central role in the hypothalamic-pituitary-gonadal-axis are *FSH* and *LH*, with the follicle-stimulating hormone inducing egg and sperm production.[47] Previous studies have reported GWAS significant associations for *FSH* and *LH* for

three variants (rs11031002, rs11031005, rs11031006) upstream of *FSHB*, encoding the β polypeptide for *FSH*.[47–49] A GWAS of *FSH* and *LH* within a sample of Chinese research participants (N=2,590) with polycystic ovary syndrome (PCOS) (N=1,882) and controls (N=708) found that top variant rs2300441, located in intron of *FSHR* led to a reduced level of *FSH* in both groups.[49]

The gene *DNAH2* (dynein axonemal heavy chain 2) is another notable reproductive trait gene. *DNAH2* harbors associations for age at menarche,[50] sex hormone binding globulin,[51] testosterone[51] and uterine fibroids[52] (GWAS catalog) while also being linked to spermatogenic failure, an autosomal recessive Mendelian disorder characterized by male infertility (OMIM).[53] The estrogen receptor 1 gene, *ESR1*, is also associated with multiple reproductive traits: age at first birth,[3,39] age at first sexual intercourse,[3] sex hormone binding globulin[54] and testosterone.[43] In OMIM, *ESR1* variants are reported to play a role in susceptibility to migraine[55] and myocardial infarction,[56] and to cause estrogen resistance.[57] Estrogen is related to regulation of the menstrual cycle, secondary sex characteristics, with declined levels linked with menopause.

MCM8 is associated with age at menopause,[50] anti Mullerian-hormone levels,[58] estradiol[59] , heavy menstrual bleeding [60]and uterine fibroids.[60] Furthermore, rare mutations in *MCM8* have been linked to premature ovarian failure (OMIM) (see **Box 3**).[61] *MCM8* has a relatively large effect on the timing of menopause, with each minor allele at *MCM8* increasing the age at menopause by around 1 year.[16]

The *WNT4* gene is associated with endometriosis, ovarian cancer, gestational duration,[62] pelvic prolapse and uterine fibroids, while a rare *WNT4* variant has been reported to cause SERKAL (SEx Reversion, Kidneys, Adrenal and Lung dysgenesis) syndrome,[63] an autosomal-recessive Mendelian disorder characterized by sex reversal as well as kidney, adrenal gland and lung anomalies. *WNT4* has also been linked to Mullerian aplasia and hyperandrogenism,[64] a disorder that affects the female reproductive system.

FTO (FTO alpha-ketoglutarate dependent dioxygenase) was found to associate with six different reproductive traits and has been found to have strong associations with body mass index, obesity risk, and type 2 diabetes. Genetic variants close to *FTO* genes increase the body weight of individuals carrying these by around one pound.[65] Obesity, which has a genetic, lifestyle and social component, has been related to reproductive success and infertility. This is due to ovulatory dysfunction related to the dysregulation of the hypothalamic-pituitary-ovarian axis, disrupted meiotic spindle formation and mitochondrial dynamics, cellular damage and altered levels of adipokines like leptin.[66]

GWAS are by nature designed to detect common genetic variants and due to the complex nature of reproductive traits and aging, each genetic variant has a small effect, but when combined can have a sizable effect. For instance, common variants of minor allele frequency (MAF) >5% have individual effect sizes of around 2 to 5 weeks for age at menarche[67] and 56 common variants predict a range from 0.07 years to 0.88 years per allele for menopause.[25] A

one standard deviation change in the age at first sexual intercourse (AFS) and age at first birth (AFB) polygenic score is associated with a 7.3 and 6.3 month delay respectively.[3] Those in the top 5% of the polygenic score for AFS are less likely to experience their sexual debut before the age of 19 and those in the top 5% for AFB are more likely to postpone first birth until around 27 years.[3] Other reported effect sizes of genes in **Table 1** [MAF >5%] are FSHB for menarche (1.5 weeks) and menopause (2.5 months) and MCM8 (10.5 months) for menopause.[15]

Despite the sizeable aggregate effect that common variants can have on reproductive traits, future association studies, which make use of enhanced phenotyping and greater statistical power, are likely to detect rare variants with even greater effects. A recent example (published after our literature search) for age at menopause analysed rare protein-coding variants in 106,973 women[196], implicating genes with effects around give times larger than previously found for common variants (*ETAA1, ZNF518A, PNPLA8, PALB2* and *SAMHD1*; not included in our results), including a 20-fold greater effect for a single variant in *ZNF518A.* Furthermore, most reproductive trait GWASs so far have been performed assuming an additive model. Novel insights can be gained through performing GWASs under alternative models. Parent-of-origin-specific allelic associations have been reported for age at menarche[67] and a recent recessive model GWAS detects a low-frequency variant in *CCDC201* that has a substantial recessive effect on age at menopause[197]. Homozygous carriers of this variant go through menopause 9 years earlier on average and consequently tend to have fewer children.

Reproductive and other health-related traits

The genetics of reproductive traits have been linked to other health traits and diseases including breast cancer, cardiovascular disease and osteoporosis[68,69] but also to behavioral and psychiatric traits.[3] In many cases, the causal relationship and underlying biological mechanisms of the associations remain unclear and there are multiple pleiotropic roles of genes related to growth, pubertal timing and disease risk.

BMI, metabolic disease and obesity-related pathways

There is considerable population variation in the age at puberty onset and menopause, the timing of which is related to health outcomes in later life. *FTO* and obesity-related pathways and reproductive aging has been linked to metabolic diseases, suggesting a shared etiological basis. An earlier age at menarche has been linked to a higher risk of obesity, type 2 diabetes mellitus and cardiovascular disease.[70] Bi-directional Mendelian randomization reveals complex pathways, with increases in BMI over time associated with earlier menarche.[71] In fact, 21 of the genes that play a role in obesity were also associated with human infertility and reproduction[72] and the GWAS locus near *LEKR1* and *CCNL1* is common to waist-to-hip ratio[73] and birth weight.[74] Leveraging whole population registers in Finland and Sweden, a recent study found that the strongest associations for remaining childless for women were endocrine-nutritional-

metabolic disorders.[75] Proposed biological mechanisms relate to leptin and the relationship to appetite suppression and specifically rare deleterious mutations in the leptin gene (LEP), associated with early onset obesity and hypogonadotropic hypogonadism.[76] Conversely, higher BMI may be protective and related to later menopause.[77,78]

Hypothalamic-pituitary-gonadal axis

Many of the GWAS loci associated with multiple reproductive traits are located in or near genes that regulate the hypothalamic-pituitary-gonadal axis. This regulates sex steroid production and fertility, largely explored in monogenic disorders such as Kallmann syndrome (see **Box 3**). Mechanisms underlying rare reproductive disorders may prove fruitful future avenues of exploration. These include rare mutations that disrupt GnRH cell function (e.g., *KISS1R, TACR3, GNRHR*), but also genes related to hypothalamus and pituitary development (*FRS3, LGR4, TBX6*) or hormone processing (*9PCSK1*, *PCKS2*).[67] There is emerging evidence of a shared etiology between reproductive traits and lipid regulation and proteins that regulate sex steroid exposure.[79] Age at menopause has also been linked with *FSHB* and circulating *FSH* level and rise in hypothalamic and pituitary hormone secretion due to loss of sex steroid feedback inhibition.[80]

Hormone-sensitive cancers

Numerous epidemiological studies have linked reproductive traits and aging to hormone-sensitive cancers such as breast, prostate or testicular, endometrial or ovarian cancer.[68] Five of our traits were associated with *ESR1*, with recurrent activating mutations within the ERα-LBD (estrogen receptor alpha-Ligand Binding Domain) found in 15-20% of patients with metastatic ER-positive endocrine-resistant breast cancer.[81] People with early puberty and delayed menopause have been shown to have a higher risk of hormone-receptor-positive breast cancer.[82] People who experience menopause later may have less efficient DNA damage response (DDR) mechanisms. For example, *CHEK2* loss of function leads to later menopause due to a failure to detect DNA damage, leading to preservation of DNA damaged oocytes.[83] This fails to explain, however, how loss of function variants in other DDR genes such as *BRCA1/2* is linked to earlier age at natural menopause.[83] A series of studies have indicated that later age at natural menopause is linked to longevity, lower morbidity, and mortality.[84–86] There appears to be an antagonistic pleiotropic relationship of cancer versus ageing and longevity, particularly with genes involved in tumor-suppression.[87] Further research is warranted examining the role of cancer and ageing and longer lifetime exposure to estrogen or progesterone.[88]

Psychiatric and behavioral traits

The genetics of behavioral and complex reproductive traits are correlated with multiple psychiatric and related behavioral traits. A recent study calculated genetic scores using LD score regression across 25 reproductive traits (e.g., age at menarche, number of children,

endometriosis) with behavioral traits such as years of education and risk tolerance, psychiatric disorders (e.g., ADHD, schizophrenia), substance use (e.g., age at initiation smoking, cannabis use) and personality (e.g., openness to experience).[3] Strong genetic correlations existed between reproductive traits themselves, with very high genetic correlations between age at first birth and educational attainment in females (0.74 ±0.01) and a negative genetic correlation with adult risk tolerance (i.e., low risk tolerance) and age at first sex and first birth (i.e., later reproductive behavior) (AFS ~ –0.40; AFB ~ –0.25). They also found a strong correlation with ADHD (AFS –0.62 ± 0.03) and age at onset of smoking (AFB 0.74 ± 0.03). Genetic factors associated with early sexual debut, teenage pregnancy and early substance use are thus to some extent shared.

Whilst previous literature has highlighted the role of diseases among women, many health-related outcomes of reproduction relate to later childbearing or childlessness and are linked to the lack of a partner or postponing parenthood.[89] A recent study of childlessness in Sweden and Finland found that singlehood was correlated with heritable mental–behavioral traits such as schizophrenia and acute alcohol intoxication, with the association more pronounced in men.[75] While different social and individual preferences for behavioral phenotypes that ultimately impact partner choice may be correlated with such mental–behavioral traits, this association provides support that individuals may ultimately inherit a common genetic liability for a spectrum of interlinked complex traits related to reproduction.

We note that particularly the genetics of complex behavioral phenotypes can be confounded by social and economic factors, including historical period and country.[90] Genetic variants associated with more children in one era could have the opposite effect in another. Those with more education tend to have less children, an association that is usually stronger for women than men.[91] This is also observed on a genetic level, i.e., the genetic components underlying number of children and educational attainment have a substantially negative correlation.[3,39] Women who have a high genetic propensity for education, have fewer children, related to multiple individual, economic and social structural reasons.[6]

An Icelandic study demonstrated that after 30 years of age, women with a high education polygenic score actually have more children than those with a low score, but given that the natural reproductive age of women has its limit around 40 years old, this is not enough to compensate for the lower number of children the high-score women have when they are younger.[91] Although the pursuit of higher education for women plays a role, when restricted to an Icelandic sub-cohort of women with 10 years of education (the legal limit), the women with a high education polygenic score still tended to have children later, with an effect that is similar to that of the whole cohort.[91] The authors hypothesized that the education genetic component is partially related to the propensity of long-term planning, and thus would have an effect on age at first child independent of the actual education attained. Furthermore, a recent study demonstrates that age at first child of women is also associated with the genetic component underlying participation in the UK Biobank.[92]

These findings show how the relationship between socioeconomic factors and the genetics of reproduction requires careful interpretation given the interrelated behavioral nature of these traits. When not properly controlled for, population stratification related to factors that can affect reproductive traits, such as education, may lead to associations that represent false positive results.[93] At the same time, associated genes may be significant but only causal insofar that they operate through other behavioral traits affecting socioeconomic factors like educational attainment, which in turn ultimately impact fertility decisions (e.g., delayed childbearing).[3] Additionally, cross-population studies have shown that genetic effects on such complex traits are to some extent not universal but specific to particular data sources,[90] likely reflecting heterogeneity in phenotypic measurement or gene–environment interactions. Discriminating between these possibilities for reproductive traits and other phenotypes influenced by demographic effects can be achieved through the use of family-based GWAS data,[94] which control for the latter. One study comparing population (between-family) within-sibship (within-family) GWAS estimates for age at first birth and number of children in turn found that estimates were attenuated by 52 and 67%, respectively.[95] Despite their complexities, the collection of further family-based genetic data can help to catalyze more within-family designs that can minimize effects of socioeconomic factors confounding associations.[94]

Reproductive aging, longevity and offspring health

Markers of reproductive aging and links with longevity

Another area of research has linked reproductive lifespan and key markers such as menarche and menopause and reproductive senescence with aging and longevity. As illustrated in **Figure 2**, standard markers of reproductive aging and fertility decline are drops in ovarian reserve (i.e., follicle number), FSH and anti-Müllerian hormone (AMH), with genetic markers in clinical tests focusing on POI. Reproductive aging research has also focused on DNA damage response (DDR) in ovarian aging.[16] A DDR pathway is one that is initiated by cells to repair DNA when they detect DNA damage, which could relate to oocyte loss during early meiosis recombination. There are relationships of early menopause and DDR-related genes, [16] with a recent study linking a wide range of DDR processes and loss-of-function (LOF) variants in key DDR-associated genes with age at menopause.[83] LOF of *CHEK2*, for instance, has previously been shown to delay menopause and increase mosaic loss of Y chromosome,[96] which is associated with increased risk of mortality and age-related diseases including multiple cancers and reduced cardiac function.[97] However, we do not know why LOF variations in other DDR genes are linked to earlier age at natural menopause.[83] As noted previously, later age at natural menopause has also been associated with longevity, lower morbidity and mortality.[85,86] Similarly, there is also an antagonistic pleiotropic relationship of cancer and longevity, and evolutionary theory provides a useful explanation for this paradoxical relationship of DDR genes in aging.[87,98]Other proposed markers include homologous recombination and meiosis pathways, DNA damage pathways, mRNA transcription and translation pathways, mitochondrial dysfunction and epigenetic aging

clocks.[99] An ongoing question related to female aging is whether people with premature ovarian aging or early menopause may also have more generalized premature aging. A recent analysis of rare protein-coding variants related to ovarian aging found that female (and male) carriers of these rare variants are at increased risk of cancer, with mutations resulting from the loss of activity of DDR components.[196] Applying 'epigenetic clocks', which are biomarkers of aging based on DNA methylation levels, another study found that increased epigenetic age acceleration (in blood) is significantly associated with earlier menopause.[100] They also found evidence of co-heritability between age at menopause and epigenetic age acceleration in blood using genetic data. Others have noted that people with Hutchinson-Gilford progeria or Werner syndrome experience hypogonadism or premature menopause, possibly linked to DDR mechanisms.[101] Several theories have also been proposed to explore the link between reproduction and accelerated aging. Prevailing evolutionary models often extend the antagonistic pleiotropy hypothesis of aging to posit a genetic trade-off between early life reproductive fitness and later life mortality,[102] especially in females, anchored in the physiological dynamics of energy allocation for reproduction and offspring survival over somatic maintenance.[103] Experimental studies using animal models have subsequently identified cases of antagonistic pleiotropy and genes co-regulating reproduction and longevity.[104] In humans, such unambiguous evidence is lacking. But an increasing number of studies have found a negative genome-wide genetic correlation between reproductive traits and lifespan.[105,106] Causal studies are needed to fully unravel the antagonistically pleiotropic variants that have been associated with regulatory effects across multiple tissues or on multiple target genes, and to understand whether comparable costs to male lifespan from reproduction exist.

The timing of puberty onset, fertility and reproductive window has also been related to longevity in diverse ways. A one standard deviation increase in the polygenic score for the timing of age of first birth was found to have a 2–4% reduction in mortality (measured by proxy of parental mortality).[3] Similarly, a genetic association between traits measuring later puberty timing in males and longer lifespan has been found to correspond to 9 months longer life per year later puberty.[107] At the same time, recent epigenetic aging research on pregnancy has found that the physiological stress of pregnancy may cause a person's biological age to increase by up to 2 years.[108,109] In comparison with other mammalian species, notably primates, humans also have long post-reproductive lifespans (see **Fig 2**). Evolutionary life-history theory has attributed this slow aging process post-reproduction to the care and investment that older family members, especially females via the 'grandmother effect'[110], provide to their descendants.[111] Further study is now needed to integrate these myriad findings.

Parent's age and de-novo mutations

As **Figure 1** illustrated, parents in many high-income countries are having their first and later children at increasingly older ages. Older parents are associated with a higher risk of preterm birth[112] and a variety of birth defects in offspring.[113] Potential biological pathways are oxidative stress, mitochondrial dysfunction, telomere shortening, chromosome errors and gene

mutations.[114] Parents' age can also have a direct biological impact on the child through *de novo* mutation events. While large scale genetic abnormalities, such as cell division errors that lead to chromosome 21 trisomy and Down syndrome are associated with advanced age of the mother,[115] advanced age of the father contributes more to the number of small point mutations.[116–118] A study of 78 Icelandic parent-offspring trios revealed correlations between paternal age with *de novo* mutations.[116] While mutations sometimes have positive effects that play a key role in human evolution, most often the functional effect is detrimental, leading to conditions that include schizophrenia[119] and autism[119] and higher risk of spontaneous miscarriage.[120] Given the sharp increase in risks for schizophrenia and autism among children conceived at older paternal age, some have proposed sperm freezing for young prospective parents to counter this effect.[121] Although there has been a focus of female reproductive aging and measurements, genetic mutations appear to exhibit more severe infertility outcomes in males. This has been related to the disparate meiotic regulatory processes in the sexes and gene mutations that have been found to cause male infertility such as azoospermia.[122]

Taken together, the above findings, and our increasing knowledge of the genetics of reproductive development, can inform our understanding of the relationship between reproduction and aging more generally in a number of ways. Research on markers of reproductive aging and fertility decline, for instance, may act as markers for aging more generally. Similarly, variants implicated with multiple reproductive traits can be studied to assess potential co-regulatory effects on aging. Finally, our knowledge of the link between parent's age and de-novo mutations in offspring can help guide research on the anticipated effects of increasing age at first birth on potential changes in specific age-related diseases over time.

Concluding remarks and outlook

GWA studies have uncovered multiple genes and variants associated with the risk of complex reproductive traits and reproductive aging. Using the GWAS Catalog as a basis, we isolated 159 relevant studies across 44 reproductive traits. By virtue of this approach, we were able to describe multiple genes that harbor association signals for four or more different reproductive traits and where there is known causal function (OMIM). Our work extends existing reviews in several ways by going beyond the examination of female[15] or male traits only,[123,124] enabling us to report genes associated with both sexes. We likewise expand phenotypes beyond infertility,[125,126] puberty and reproductive lifespan to a broader phenotypic spectrum of reproductive traits and behavior.

Although the review has novel strengths, there are also limitations. We provide an overview of findings and a gene list, but a systematic analysis and assessment of the biological processes and translation into clinical practice is outside of scope. In our analysis of gene-phenotype associations we rely on the gene mapping pipeline of GWAS catalog. Given multiple phenotypes, we were unable to engage in a robust analysis of each disease's etiology, gene

structure, function, previously identified and related variants or disease mechanisms. Also outside of scope were identification of genetic diseases that are transmissible to offspring and may impact reproductive or infertility-related comorbidities. Finally, attributing a genetic cause to a particular reproductive trait or aging is also contingent upon multiple confounding factors beyond genetics including the patient's medical history, lifestyle and social and economic environment.

Open questions and remaining challenges

Male reproduction

The majority of research on reproductive genetics and reproduction in general has focused on female individuals and when male individuals are included, it is often smaller or select samples. Yet, fully understanding the correlates, causes and consequences of reproductive aging requires collecting more data on male reproductive traits and improving our understanding of etiology of male reproductive health and reproductive aging,[125] but also couple and parental dynamics and increased paternal caregiving.[127] The last decade has seen important advancements, particularly in research on male factor infertility, and efforts by consortia like the Male Reproductive Health Initiative.[128] Over 50% of male infertility has, however, been categorized as idiopathic with unknown causes.[129] The startling lack of progress in topics such as male contraception, the interplay between male reproductive and mental health[130] and the continued clinical underdiagnoses of male infertility suggest more work is needed.

Beyond European ancestry and WEIRD populations

GWAS research in general has disproportionality focused on European ancestry populations[131] and the majority of studies we evaluated drew from European-ancestry populations in Western, Educated, Industrialized, Rich, and Democratic ('WEIRD') countries.[132] Although common across GWASs,[131,133] the inclusion of under-served ancestries and geographical regions will provide a more accurate picture of reproductive aging, and how it varies across contexts.[90] This is especially relevant in the study of gene–environment interactions, as WEIRD countries, but also the selection of higher socioeconomic individuals into studies, impacts genetic results.[90,92] This can influence our understanding, treatment and diagnosis of reproductive care and exacerbate inequalities. The need for improved knowledge of certain fertility-related outcomes (e.g., the effect of offspring number on longevity) is also more pressing in high fertility contexts.

Achieving greater diversity in reproductive research will accelerate scientific discovery and improve translation efforts. For instance, a recent study examining infertility in men in Estonia uncovered unfavorable Y-chromosomal variants linked to impaired spermatogenesis.[134] The subtype, which has a nine fold increase in the risk of fertility issues, is carried by a large number of people of European ancestry, ranging from around 5-6% of people with Y-chromosomes (i.e., men, see Box 2) in Estonia but up to 20% in Poland and Czechia. GWAS have focused on

common variants, but the rise of whole genome sequencing and additional technological developments in combination with expansion to diverse populations, will bring more rare or low-frequency variant discoveries. The genetic correlations observed between traits across multiple loci are promising for further targeted examinations that could potentially lead to molecular genetic diagnoses or drug targets. Institutions and funders need to structurally intervene at various steps in the research cycle—from recruiting more diverse participants and providing dedicated funding to formulating novel research questions (i.e., ones that more precisely assess different environmental risk factors) – to increasing diversity among researchers.[133] The potential benefits are myriad, serving both science and society.

Early-life, environmental exposures and epigenetics

Unequal living environments also impact detection and prevalence of reproductive outcomes. A systematic review found that the prevalence of uterine fibroids was consistently higher in Black compared to White people, likely related to disproportionate experiences of a range of exposures across their life course.[135] Environmental conditions such as early-life childhood events also have the potential to impact age of pubertal onset, hormone levels and other reproductive traits. Animal and cell models have been developed to study the role of the epigenome and key windows of susceptibility in early development that in turn can reprogram reproductive function.[136] The study of epigenetic modifications in regulating reproductive onset and lifespan as an adaptive response is thus a promising area. It would, however, still face the common challenges of identifying appropriate proxy tissues and determining the causal effect with interrelated hormones that impact the epigenome and epigenetic aging.

Relatedly, increasing evidence points towards a link between adverse reproductive health outcomes, especially in relation to subfertility and pregnancy complications, and various chemical and physical exposures in the built environment, such as synthetic toxins including pesticides, plastic compounds, heavy metals, and air pollution,[137,138] as well as factors like shift work, overwork, or stress.[139] A common hypothesis suggests that each of these reproductive toxicants impact reproductive health by acting as endocrine-disruptors, mimicking or inhibiting endogenous hormones, and thereby interfering with hormone production.[140] Studies have shown that in low-fertility countries like Korea (**Fig 1.**), phthalates, chemicals used in plastics production that act as powerful endocrine disruptors, are significantly higher in patients with advanced-stage endometriosis.[141] However, most studies currently only provide correlational evidence and more investigation can identify plausible causal pathways. This will arguably become an increasingly important topic as more countries industrialize and amass chemicals and other toxicants harmful to reproductive health.[142] There is also a growing body of animal studies which has shown that gut bacteria can mediate the association between environmental exposures, pregnancy outcomes, and offspring health.[143,144] If this mechanism is validated in humans, it may advance the possibility of potentially modifiable preconception factors.

Biology, exome/genome sequencing, drug targets and interventions

Although we strived to highlight potential causal variants uncovered from genetic discoveries, the majority of research in this area finds associations. Biological insights of the processes and mechanisms underlying gene discovery has the potential to provide drug targets. It remains challenging to identify functional biological effects and determine which genes and pathways are responsible for reproductive trait outcomes. A longstanding belief of reproductive biology is that oocytes apoptose from fetal development to menopause, but the presence of stem cells in ovaries could be a promising way forward to activate oogenesis in people with lower ovarian reserves. Further research can also explore functional aspects of FSHB promoter regulation and FSH concentrations on reproductive outcomes and diseases. For instance, compared to people who carry the FSH GG genotype at rs10835638, those with the decreasing GT genotype were found to respond poorly to ovarian hyperstimulation (47.5% compared to 26.5%, p=0.010).[145]. Examining the genetic basis of ovulation in cases of 'super fecundity' such as dizygotic twinning or extending reproductive hormone traits to examine progesterone are other promising innovations. More research is also required to understand how the timing of age at menarche and menopause relates to multiple aspects of human health, morbidity, mortality and longevity.[85] Timely diagnosis of disease, infertility and reproductive lifespan are also vital extensions. Diseases such as endometriosis take on average 8 to 10 years to diagnosis.[146] As noted throughout, research into male and joint parental reproductive health remains a vital frontier. Finally, large-scale exome/genome sequencing is another emerging area of innovation. A recent study found that individuals who carry loss-of-function mutations in *MC3R* (including a rare homozygote individual), have a later onset of puberty and sexual maturation.[147] Whilst two recent analyses of rare variants found several genetic variants that affect how quickly fertility ends, including in ZNF518A that reduces reproductive span by six years[196,197].

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Box 1: Glossary of selected reproductive terms

- **Reproduction:** All biological and behavioral processes related to the production of offspring. In humans, reproduction begins with fertilization, typically as a result of sexual intercourse or in vitro fertilization.
- **Reproductive behavior:** Behaviors related to reproduction that include all aspects of finding a partner(s), sexual reproduction, pregnancy and the care and nurturing of offspring and family relatives.
- **Reproductive lifespan:** The time between the onset of puberty and end of reproductive period, people with ovaries marked by oocyte depletion and menopause and for people with testes, often decrease in sperm production and function.
- **Reproductive traits:** Traits associated with reproductive lifespan and aging (such as age at menarche, voice breaking, menopause), reproductive behavior (such as age at first sex or birth), infertility or those affecting lifespan or health outcomes (such as endometriosis) and related hormonal concentration (such as oestradiol).
- **Fecundity:** The biological capacity for reproduction, irrespective of the intentions to reproduce. Fecundity can be measured for a given population or for individuals.
- **Fecundability:** A measure of fecundity is usually defined as the probability of pregnancy during one month or one menstrual cycle.
- **Fertilization:** The molecular event whereby an ovum and sperm, reproductive cells, fuse to form a zygote.
- **Fertility:** The ability of an individual or partners to engage in reproduction. In medicine, fertility refers to the ability of parents to conceive and have offspring given unprotected intercourse, which in demography is termed infecundity or sterility. Demographers define fertility often as the tempo of childbearing (different ages at having children), spacing and quantum (live children born during a certain period).
- **Total fertility rate:** A measure of age-specific birth rates for a given population, usually defined as the number of births per female of reproductive age in a single country for a specific period of time.
- **Infertility:** The inability to establish a pregnancy after 12 months of regular and unprotected sexual intercourse.
- **Childlessness:** Describes individuals who have had no live-born children by the end of their reproductive lifespan (often defined as age 45 in females and 55 in males). Childlessness includes being voluntarily childfree (choice, preference) or involuntary childless (e.g., infertility) or a mix of the two (i.e., postponed and then faced with fecundity challenges, infertility).
- **Menarche:** The onset of menstruation, the first menstrual cycle.
- **Menopause:** The cessation of menstruation due to loss of ovarian follicular activity.
- **Spermatogenesis:** The onset of the production of sperm, needed for fertilization.
- **Semen parameters:** A measured factor collected during semen analysis to evaluate male fertility. The main three parameters are the concentration of the spermatozoa in the semen, their motility and their morphology.
- **Assisted reproductive technology (ART):** Any procedure that involves the

manipulation of eggs or embryos (such as in vitro fertilization), typically used to treat infertility.

- **In vitro fertilization (IVF):** The removal and fertilization of an egg from the ovary with sperm in a laboratory setting to form embryos.

Box 2: A note on terms related to sex, gender and reproduction

Throughout this paper, in our discussion of genetics analyses we use the terms 'female' to describe individuals who have XX chromosomes and 'male' to describe individuals who have XY chromosomes. Given we use results from secondary data, our assumption is that given these individuals were classified in this way in the respective analysis, they are likely to identify with the assigned sex indicated in the analysis and assigned female/male at birth and identify with their assigned sex. This reflects the terms used in the studies on the genetic basis of reproductive traits we review, which are all conducted on individuals with either XX or XY chromosomes, and do not include individuals with, for instance, XXY chromosomes, intersex individuals or those who do not identify with the sex they were assigned at birth. At times we also describe multiple reproductive traits (e.g., age at menarche, endometriosis, miscarriage) as female/male traits for fluency and to make comparisons,[148] while acknowledging that no one trait determines whether a person is male or female.[149]

Additionally, when discussing reproductive and behavioral traits where an individual's gender identity plays a significant role, we avoid the terms male/female to not conflate sex and gender and seek to provide the context of the discussed study or adopt the terms used (e.g., 'men', 'women') for fluency and unambiguity.[148] Similarly, we use the terms 'mother' and 'paternal' whilst acknowledging that not all birthing or parenting individuals choose these labels.

As with the genetic studies we cite, a limitation of our work is that is does not include individuals who do not identify with the sex they were assigned at birth.

Box 3: Monogenic and rare reproductive disorders

Genetic disorders, which are chromosome changes and monogenic disorders, account for 5–10% of female infertility and subfertility.[150] Unique gene-disease pairs related to reproductive failure, including the impaired ability to conceive, but also to carry a term pregnancy. Around 4% of infertile male individuals have a diagnosis of a genetic cause, with the majority remaining unclassified or unexplained.[124]

There are established genetic components of male infertility including Klinefelter syndrome, Y-chromosome microdeletions, Robertsonian translocation, XX male, azoospermic factor (AZF) deletions.

For female individuals, rare Mendelian disorders have been related to idiopathic hypogonadotropic hypogonadism (IHH),[151] where around 30–40% are explained by these gene defects. Others have examined primary ovarian insufficiency (POI)[152] showing triplet repeats in FMR1 or X-chromosomal abnormalities (around 5% of patients).

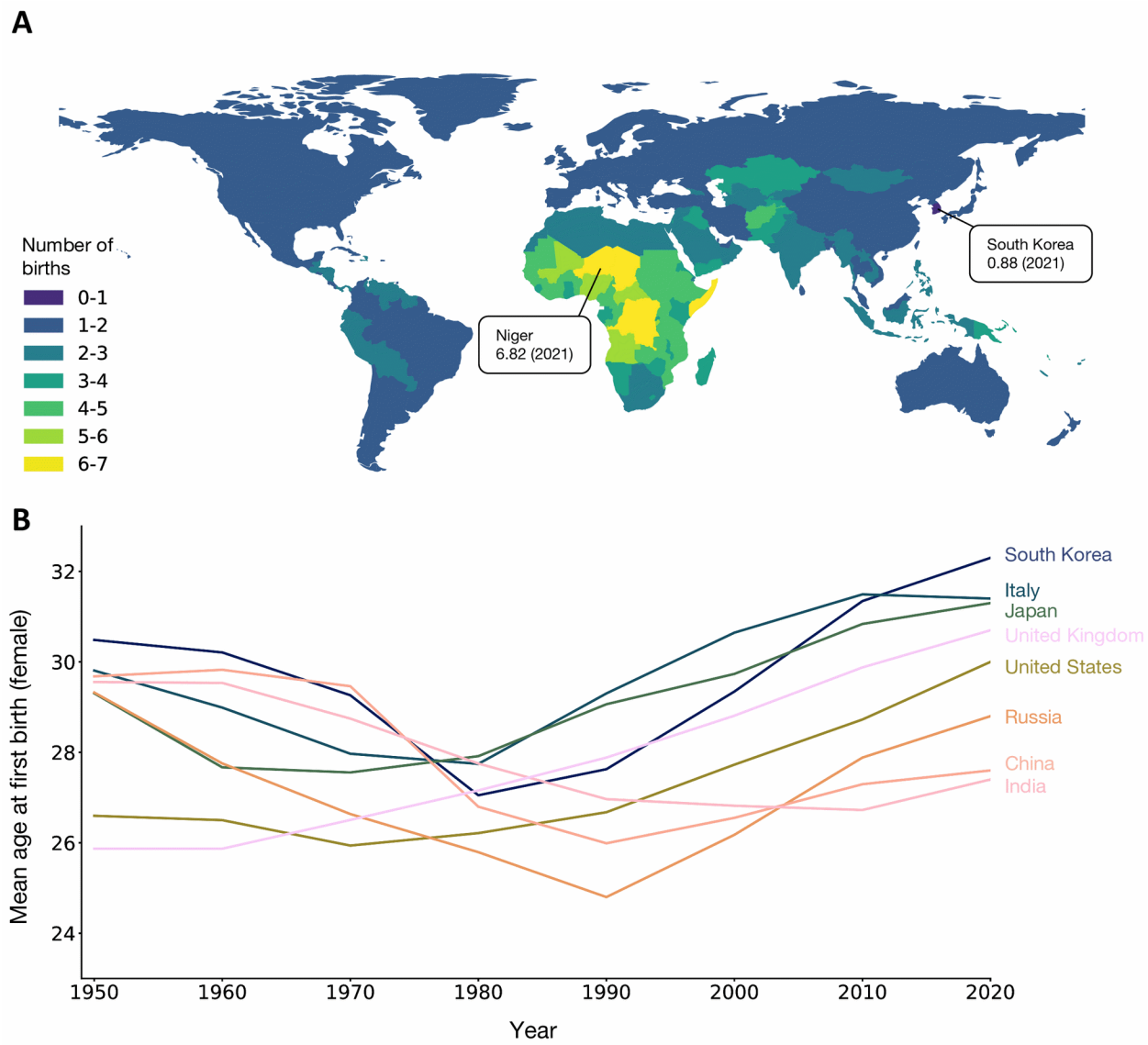

Fig. 1 | Total female fertility rate and change in mean age at first birth. (A) Total fertility rate across the world, expressed as the number of children per female, based on age-specific fertility rates in 2021. Annotated countries South Korea and Niger have the lowest and highest fertility rate, respectively. (B) Changes in average childbearing age (1950–2020), the mean age at

which female individuals have their first child. Estimates are based on age-specific fertility rates of first-born children in one particular year. Data sources Fig 1A,[153] Fig 1B.[154–158]

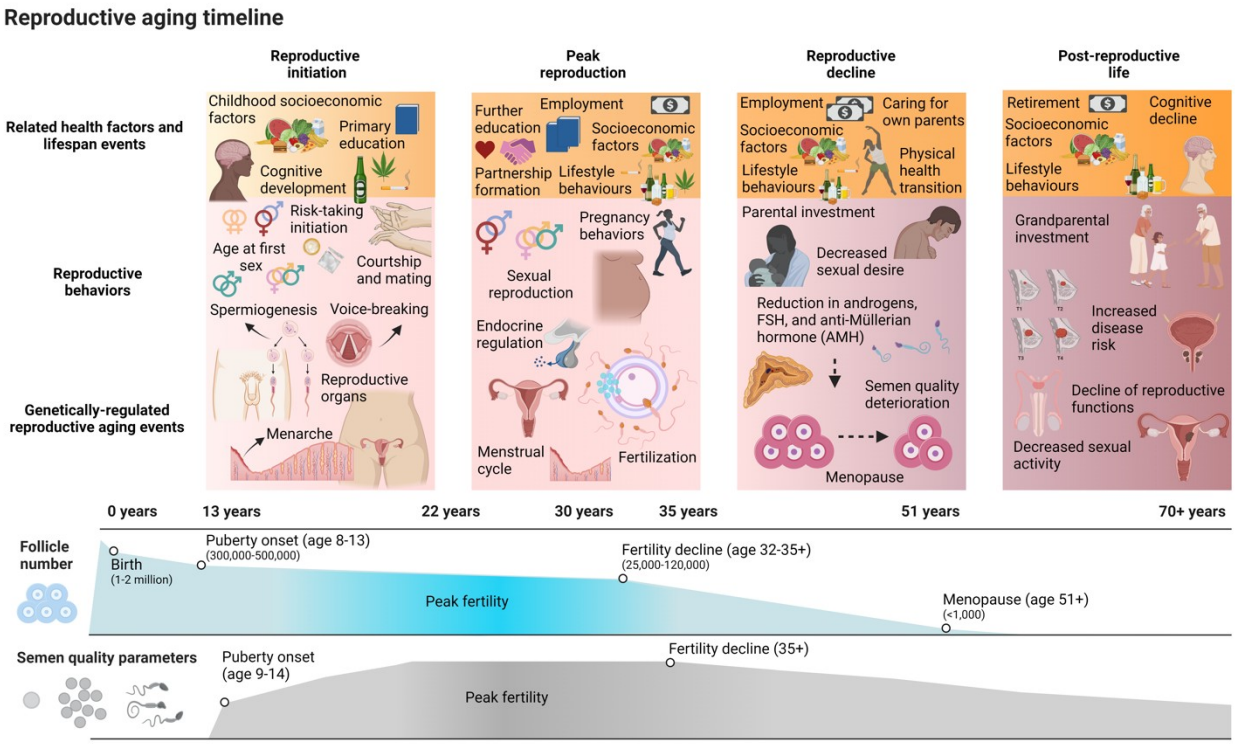

Fig. 2 | A life course timeline of reproductive aging. Reproductive aging is a multi-stage process that includes reproductive initiation during puberty onset, peak reproduction (when fertility is biologically optimal), alongside post-reproductive transition and post-reproductive life stages. Most studies examine the period during which individuals are capable of pregnancy or fathering their own offspring as the window of analysis. Yet, since reproduction-related events and behaviors like age at first birth are associated with longevity, a life course perspective demonstrates how the genetics of reproduction, reproductive behaviors and health are related.

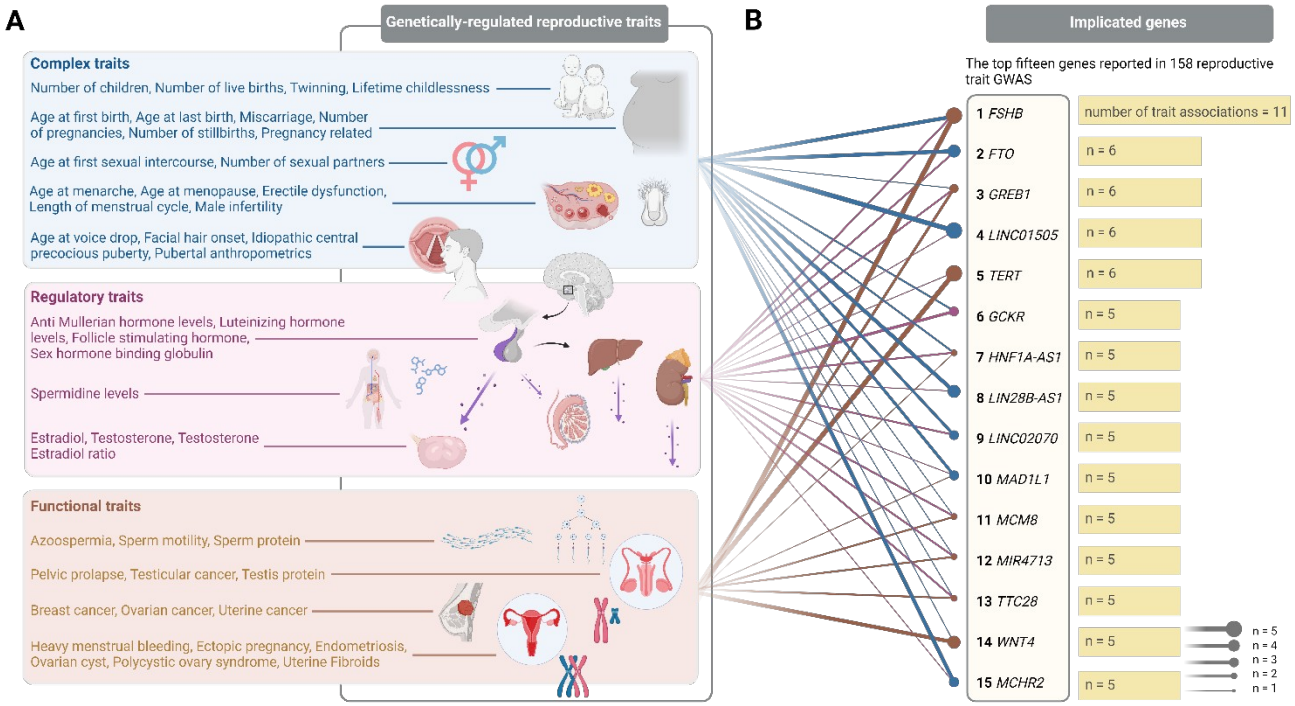

Fig. 3 | Genetically-regulated reproductive traits. (A) List of the 44 genetically-regulated reproductive traits that we consider in this review, and for which GWAS have been conducted, grouped into three broad categories for illustrative purposes: Complex, regulatory and functional traits. (B) The top 15 implicated genes reported for the traits we review ordered by the number of trait associations (see **Table 1** for all implicated genes that are reviewed). Genes are connected to reproductive trait categories with line width indicating number of trait associations per category.

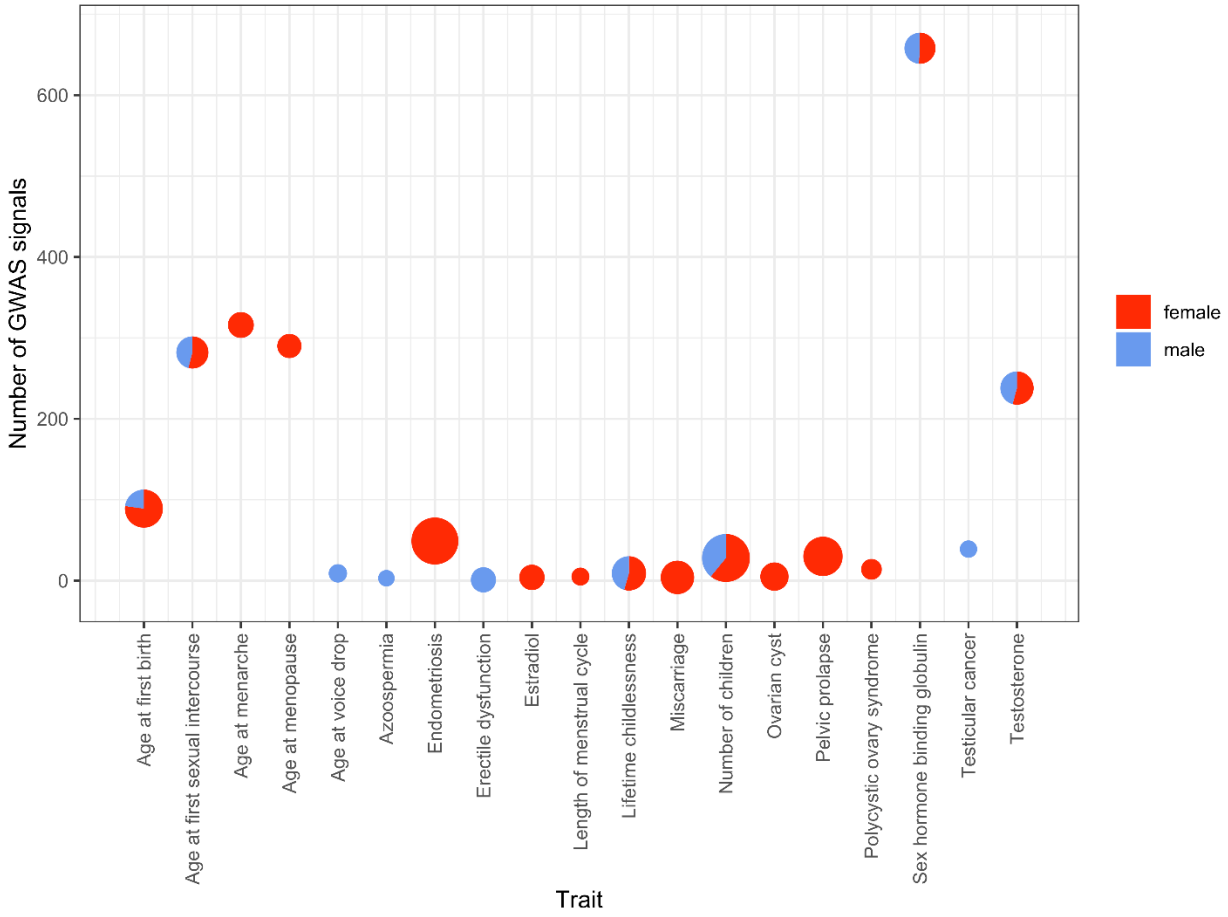

Fig 4. | Reproductive trait GWASs, sex-specific sample sizes and number of independent signals. Figure shows number of reported independent association signals for a range of reproductive trait studies found in the GWAS catalog (as of 5 May 2024). The number of independent signals and female/male sample sizes were manually curated from either text or table in each study. For each trait, the study with the biggest reported initial sample size in GWAS catalog is depicted, except for age at menopause, polycystic ovary syndrome, testicular cancer and age at voice drop where the second biggest studies are depicted as well as sex

hormone binding globulin where the fourth biggest study is depicted, as information about independent signals, sample size and/or female/male ratio were easily tractable from those manuscripts. The size of the pies represents sample size (N). For case/control traits the sample size is N=cases+controls. The traits depicted are as follows: Age at first birth (N=542,766);[3] Age at first sexual intercourse (N=397,338),[3] Age at menarche (N=242,000);[50] Age at menopause (N=201,323);[83] Age at voice drop (N=55,871);[159] Azoospermia (N=8,661);[160] Endometriosis (N=762,600),[161] Erectile dysfunction (N=223,805);[162] Estradiol (N=229,966);[59] Length of menstrual cycle (N=44,871);[163] Lifetime childlessness (N=450,082);[5] Miscarriage (N=429,273);[44] Number of children (N=785,604);[5] Ovarian cyst (N=301,230);[164] Polycystic ovarian syndrome (N=113,238);[165] Pelvic prolapse (N=574,377);[166] Sex hormone binding globulin (N=370,199);[167] Testicular cancer (N=30,401);[168] Testosterone (N=424,907).[167]

Table 1 | Top GWAS reproductive trait genes.

Mapped Gene	GWAS phenotypes	OMIM/Ensembl	N
ARL14EP-DT	Age at menarche; Age at menopause; Endometriosis; Heavy menstrual bleeding, Luteinizing hormone levels; Length of menstrual cycle; Ovarian cyst; Polycystic ovary syndrome; Testosterone; Twinning; Uterine fibroids.	*ARL14EP-DT* is a long non-coding RNA gene that overlaps with the protein-coding follicle stimulating hormone subunit beta gene (*FSHB*).[169] ***FSHB*** has been linked to hypogonadotropic hypogonadism[170,171] (OMIM: 136530).	11
FTO	Age at menarche; Age at menopause; Number of sexual partners; Pregnancy related; Sex hormone binding globulin; Testosterone	*FTO* has been linked to an autosomal recessive growth retardation and developmental delay disorder.[172] A common *FTO* variant has been reported to associate with obesity[173] (OMIM: 610966).	6
GREB1	Age at menarche; Endometriosis; Ovarian cyst; Sex hormone binding globulin; Testosterone; Uterine fibroids.	Expression analysis suggest that *GREB1* is a primary target for estrogen receptor regulation[174] (OMIM: 611736).	6
LINC01505	Age at first sexual intercourse; Age at menarche; Age at menopause; Age at voice drop; Facial hair onset; Testosterone.	*LINC01505* is a long non-coding RNA gene.[169]	6
TERT	Heavy menstrual bleeding; Ovarian cancer; Ovarian cyst; Sex hormone binding globulin; Testicular cancer; Uterine fibroids.	*TERT* has been linked to leukemia[175], melanoma,[176] dyskeratosis congenita[177], pulmonary fibrosis and/or bone marrow failure syndrome[178,179] (OMIM: 187270).	6
GCKR	Estradiol; Facial hair onset; Pregnancy related; Sex hormone binding globulin; Testosterone.	*GCKR* is associated with fasting plasma glucose levels[180](OMIM: 600842).	5
HNF1A-AS1	Age at first birth; Age at menarche; Ovarian cancer; Sex hormone binding globulin; Testosterone.	*HNF1A-AS1* overlaps with the protein-coding *HNF1A* gene (HNF1 homeobox A) that has been linked to diabetes, hepatic adenoma, and renal cell carcinoma[181] (OMIM: 142410).	5
LIN28B-AS1	Age at menarche; Age at voice drop; Facial hair onset; Pubertal anthropometrics; Testosterone.	*LIN28B-AS1* overlaps with the protein coding lin-28 homolog B gene (*LIN28B)*.[169]	5
LINC02070, VGLL3	Age at first sexual intercourse; Age at menarche; Pubertal anthropometrics; Sex hormone binding globulin; Testosterone.	*LINC02070* is a long non-coding RNA gene.[169]	5
MAD1L1	Age at first sexual intercourse; Age at menarche; Number of sexual partners; Sex hormone binding globulin; Testicular cancer.	*MAD1L1* has been linked to lymphoma, B-cell, somatic,[182] prostate cancer, somatic[182] and mosaic variegated aneuploidy syndrome 7[183] (OMIM: 602686).	5
MCM8	Age at menopause; Anti Mullerian hormone levels; Estradiol; Heavy menstrual bleeding; Uterine fibroids.	***MCM8*** has been linked to premature ovarian failure[184] (OMIM: 608187).	5
MIR4713HG, CYP19A1	Estradiol; Sex hormone binding globulin; Testosterone; Testosterone Estradiol ratio; Uterine cancer.	***CYP19A1*** has been linked to aromatase deficiency[185] and aromatase excess syndrome[174,186] (OMIM: 107910).	5
TTC28	Age at menopause; Ovarian cancer; Ovarian cyst; Sex hormone binding globulin; Testosterone.	*TTC28* plays an important role in cytokinesis[187] (OMIM: 615098).	5
WNT4	Endometriosis; Ovarian cancer; Pelvic prolapse; Pregnancy related; Uterine fibroids.	***WNT4*** has been linked to SERKAL syndrome.[63] ***WNT4*** has also been linked to Mullerian aplasia and hyperandrogenism (OMIM: 603490).	5
MCHR2, Y_RNA.	Age at first sexual intercourse; Age at menarche; Age at voice drop; Facial hair onset; Testosterone.	*MCHR2* plays an important part in the control of feeding behaviors and energy metabolism[188] (OMIM: 606111).	5
BRWD1	Age at first sexual intercourse, Age at menarche; Sex hormone binding globulin; Testosterone.	It has been proposed that ***BRWD1*** is involved in chromatin remodeling.[189] ***BRWD1*** has been linked to ciliary dyskinesia, a disorder characterized with male infertility due to multiple abnormalities in the sperm flagella[190] (OMIM: 617824).	4
DNAH2	Age at menarche; Sex hormone binding globulin; Testosterone; Uterine fibroids.	***DNAH2*** has been linked to spermatogenic failure, a disorder characterized by male infertility[53] (OMIM: 603333).	4
ESR1	Age at first birth; Age at first sexual intercourse; Sex hormone binding globulin; Testosterone.	***ESR1*** has been associated with migraines,[55] myocardial infarction[191] and estrogen resistance[192] (OMIM: 133430).	4
IGSF1	Age at first birth; Age at first sexual intercourse; Age at menarche; Age at voice drop.	***IGSF1*** has been linked to hypothyroidism, central, and testicular enlargement (CHTE)[193] (OMIM: 300137).	4
PTPRF	Number of sexual partners; Pregnancy related; Sex hormone binding globulin; Testosterone.	***PTPRF*** has been linked to aplasia or hypoplasia of breasts and/or nipples[194] (OMIM: 179590).	4
THRB	Age at menarche; Sex hormone binding globulin; Testosterone; Uterine fibroids.	***THRB*** has been linked to thyroid hormone resistance[195] (OMIM: 190160)	4

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All authors planned and jointly prepared the material and revised the manuscript. MCM wrote the initial draft. SB engaged in the GWAS summaries and related graphics and VJS produced graphics and work in relation to men's fertility and environment.

Competing interests:
MCM is a Trustee of the UK Biobank, on the Scientific Advisory Boards of Our Future Health and Lifelines Biobank and on the Data Management Advisory Board of the Health and Retirement Survey. SB is a part of a working group called Alzheimer diagnostics that has received a grant from the Icelandic Technology Development fund. The remaining authors declare no competing interests.

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Supplementary Table 1. Detailed summary of reproductive trait GWASs (N=194), 2007-March 2024, GWAS Catalog

Supplementary Table 2. Categorisation of detailed disease trait mapped to 44 reproductive traits

Supplementary Table 3. Mapped Gene and Full Gene Name mapped to reproductive traits, including sample size (N) and PMID (PubMed Identifier)