Identification of 371 genetic variants for age at first sex and birth linked to externalising behaviour

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Age at first sexual intercourse and age at first birth have implications for health and evolutionary fitness. In this genome-wide association study (age at first sexual intercourse, \( N = 387,338 \); age at first birth, \( N = 542,901 \)), we identify 371 single-nucleotide polymorphisms, 11 sex-specific, with a 5–6% polygenic score prediction. Heritability of age at first birth shifted from 9% (CI = 4–14%) for women born in 1940 to 22% (CI = 19–25%) for those born in 1965. Signals are driven by the genetics of reproductive biology and externalising behaviour, with key genes related to follicle stimulating hormone (FSHβ), implantation (ESR1), infertility and spermatid differentiation. Our findings suggest that polycystic ovarian syndrome may lead to later age at first birth, linking with infertility. Late age at first birth is associated with parental longevity and reduced incidence of type 2 diabetes and cardiovascular disease. Higher childhood socioeconomic circumstances and those in the highest polygenic score decile (90%-+) experience markedly later reproductive onset. Results are relevant for improving teenage and late-life health, understanding longevity and guiding experimentation into mechanisms of infertility.

The timing of onset of human reproductive behaviour as measured by age at first sexual intercourse (AFS) and age at first birth (AFB) has implications for reproductive health, adolescent development and evolutionary fitness. First sexual intercourse has occurred increasingly earlier, by the age of 16 years for one-third of contemporary UK teenagers1. Early reproductive onset is associated with teenage pregnancy1 but also adverse health outcomes such as cervical cancer, depression, sexually transmitted diseases2 and substance use disorders3. In contrast to earlier sexual debut, we have witnessed progressively later ages at first birth for women, now reaching an average of 30 years in many modern societies and even later for men (Supplementary Fig. 3). Late reproductive behaviour is associated with lower fecundity and subfertility4 and infertility traits such as endometriosis and early menopause5,6, with over 20% of women born after 1970 in many modern countries now remaining childless7. Earlier ages at sexual debut and later ages at first birth have marked the decoupling of reproduction from sexual behaviour in many contemporary societies, with implications for sexual, reproductive and later-life health (Supplementary Fig. 2).

Since reproductive behaviour is shaped by biology and environment, a multidisciplinary approach is required to understand the common genetic aetiology and how it relates to health, reproductive biology, environment and externalising behaviour1. Since the onset of reproductive behaviour generally occurs in adolescence to early adulthood, it is often linked to externalising behaviour such as self-control and psychiatric (for example, attention deficit hyperactivity disorder (ADHD)) and substance use disorders (for example, smoking, alcohol use), often moderated by the environment (for example, childhood socioeconomic conditions). Furthermore, it may be that individuals inherit a common genetic liability for a spectrum of interlinked complex traits related to reproduction, health and longevity. There has been limited attention to understanding how these genetic effects are stratified by sex or across different socioeconomic and historical contexts.

In a previous genome-wide association study (GWAS) of AFS (\( n = 125,667 \))10 and AFB (\( n = 343,072 \)), we identified 38 and 10 novel independently associated single-nucleotide polymorphisms (SNPs), respectively. The current study includes a markedly expanded sample size for AFS (\( N = 387,338 \)) and AFB (\( N = 542,901 \)), uncovering 371 autosomal or X chromosomal SNPs, some of which are sex-specific, with 99 candidate genes expressed at the protein level in the brain, glands and reproductive organs. The multiple...
Methods applied in this study (Supplementary Fig. 1) reveal underlying genetic drivers, common genetic liabilities, heterogeneity by childhood socioeconomic status and historical period and further evidence of the relationship of later reproductive onset with fewer later-life metabolic life diseases and increased longevity.

Results

Changes in reproductive behaviour and heritability over time.

We first examine phenotypic changes in human reproductive behaviour and heritability over time. Descriptive analyses using the UK Biobank illustrate shifts in the mean AFS and AFB, changes in the shape of the distribution by birth cohort and a bi-modal distribution of AFS in earlier cohorts (Fig. 1a and Supplementary Fig. 3). Whereas AFB was often in the early 20s for older birth cohorts, this distribution has spread and shifted to older ages over time, with a marked drop in Pearson’s correlation between AFS and AFB from those born <1941 (0.60) to those born >1960 (0.31) (Supplementary Fig. 2). Using genome-based restricted maximum likelihood (GREML)\cite{11,12}, we found a steady increase in SNP heritability by birth cohort for AFB for women from 9% [CI 4–14%] for those born in 1940, climbing to around 22% [19–25%] for the latest cohorts born in 1965. For AFS, heritability ranges between 12% [7–18%] for women born around 1940 and 23% [17–28%] for men born around 1940, with a trend for women similar to AFB and a suggestive U-shaped trend for men (Fig. 1b for women and Supplementary Fig. 1B for men).

Meta-analysis of GWAS on human reproductive behaviour.

We conducted a meta-analysis of GWAS results from 36 cohorts for AFS and AFB in individuals of European ancestry (defined by genetic principal components). We imputed to the 1000 Genomes Project reference panel in a pooled sample and then stratified the analysis by sex (Supplementary Tables 1–8). In total, we discovered 371 associated SNPs. The GWAS of AFS identified 282 (272 pooled of which 4 on the X chromosome; 2 women; 8 men) SNPs at genome-wide significance (P < 5 × 10^{-8}, Supplementary Fig. 5A–C and Supplementary Table 10). The GWAS of AFB identified 89 (84 pooled of which 4 on the X chromosome; 1 women) independent SNPs at genome-wide significance (P < 5 × 10^{-8}, Supplementary Fig. 6A–C and Supplementary Table 9). The distribution of genome-wide test statistics for AFS and AFB showed significant inflation (λ_{GC} = 1.84 and 1.47, respectively), however linkage disequilibrium (LD) score regression showed that this could be attributed almost entirely to polygenicity rather than to population substructure (LD intercept AFS 1.07 (s.e. 0.01), AFB 1.03 (s.e. 0.01); Supplementary Sect. 6). The LD score intercept test confirmed that only a very small percentage (5.5%) of the observed inflation in the mean χ² statistic was due to population stratification or other confounders, rather than to a polygenic signal.
Articles

Polygenic score prediction. We then calculated polygenic scores (PGSs) using three different specifications (Fig. 2 and Supplementary Sect. 5). To validate the performance of the PGSs, we performed out-of-sample prediction in National Longitudinal Study of Adolescence to Adult Health (Add Health, a survey of adolescence to young adulthood in the United States) and UK Household Longitudinal Study - Understanding Society (UKHLS, a representative survey of adults in the United Kingdom) cohorts using ordinary least-squares regression models and report the $R^2$ as a measure of goodness of fit of the model (Fig. 2). PGSs including all SNPs explain up to 5.8% of the variance for AFS and 4.8% for AFB. The difference between the out-of sample prediction in UKHLS and Add Health is related to heterogeneity between the initial GWAS sample, including a large UK older population from the UK Biobank, which is more comparable to the UKHLS population. Add Health participants also have higher levels of right censoring (that is, not yet experienced a birth). Previous research has demonstrated that meta-analyses of complex behavioural traits using populations from diverse national contexts and birth cohorts can be influenced by this hidden heritability. A one s.d. change in the AFS/AFB PGS is associated with a 7.3 and 6.3 month delay in AFS and AFB, respectively. We then ran survival models to account for right censoring, which occurs when an individual does not experience the event of first sex or birth by the time of the interview. Using Add Health data, we estimated nonparametric hazard functions and then compared individuals at the top and bottom 5% of the PGS (Fig. 1c for AFS and Fig. 1d for AFB for women; Supplementary Figs. 8 and 9 for men). Those in the top 5% PGS for AFS (that is, genetic association with later AFS) are less likely to have their sexual debut before age 19 years. AFS PGSs appear more relevant in explaining women’s AFS in comparison with men’s. Those in the top 5% PGS for AFB (that is, genetic association with later AFB) postpone AFB across all ages until approximately age 27 years, with similar curves for both sexes.

We next examined whether these genetic effects were environmentally moderated by childhood socioeconomic status. Disadvantaged socioeconomic status is highly related to early sexual behaviour and teenage pregnancy. To explore the impact of environmentally moderated parental genetic effects on our PGSs, we examined PGS prediction across low (0–10%), medium (50–60%) and high (90–100%) PGS percentiles by parents’ education (college versus no college) as a proxy for childhood socioeconomic status. Indeed, those in the highest decile of the PGS (90–100%) for later AFB have a higher AFB, particularly past age 27 years, which is accentuated for those with highly educated parents (Supplementary Fig. 10A). Being in the highest PGS decile for AFS is associated with later sexual intercourse (a difference between highest and lowest decile of 2.08 years), especially for those from highest socioeconomic childhood households (2.39 years difference among high socioeconomic status, compared with 1.62 years for low socioeconomic status families) (Supplementary Fig. 10B).
Genetic correlations. To test the relationships of AFS and AFB with related phenotypes, we calculated genetic correlations using LD score regression\textsuperscript{15} (Fig. 3, Supplementary Figs. 11 and 13 and Supplementary Table 11). Given previous evidence\textsuperscript{8}, we examined 25 traits by sex from six relevant categories, including reproductive (for example, age at menarche, number of sexual partners), infertility (for example, endometriosis and severe endometriosis), behavioural (for example, years of education, risk tolerance), psychiatric disorders (for example, ADHD, schizophrenia), substance use (for example, age of initiation of smoking, cannabis use), personality (for example, openness to experience) and anthropometric (for example, body mass index (BMI), height). Logically, the strongest genetic correlations were observed for reproductive traits, particularly for number of children ever born (NEB). We remain cautious regarding the estimates of endometriosis considering the smaller sample size and larger confidence intervals (CIs) of our estimates. In our Mendelian randomization (MR) analysis, discussed shortly, we explore the relationship with infertility in more detail. Behavioural traits also show strong genetic correlations, particularly with AFB and educational attainment in women (0.74 ± 0.01), compared with AFS (0.53 ± 0.01). There was also a negative genetic correlation between adult risk tolerance and AFS/AFB (AFS ≈ −0.40; AFB ≈ −0.25); that is, a low genetic association with risk tolerance corresponds to a genetic association with later reproductive behaviour.

Amongst psychiatric traits, often related to externalising behaviour, the strongest correlation was with ADHD (AFS females −0.58 ± 0.03, males −0.61 ± 0.03; AFB females −0.63 ± 0.03; males −0.68 ± 0.09) and major depressive disorder (AFS females −0.37 ± 0.03, males −0.32 ± 0.03; AFB females −0.42 ± 0.03; AFB males −0.33 ± 0.08). We also observed strong genetic correlations with age at onset of smoking (AFS ≈ 0.68 ± 0.03; AFB ≈ 0.74 ± 0.03), a trait that provides a unique window into adolescent substance use and externalising behaviour around the same time as early reproductive behaviour. Genetic factors associated with early smoking, early sexual debut and teenage pregnancy are thus (to some extent) shared. As shown in Fig. 3, there are few sex differences in these correlations, with the exception of small variations in number of children, anorexia and openness to experience.

Aetiology and causality. To explore aetiology and causality, we employed GenomicSEM, exploratory factor analysis (EFA) and bi-directional MR. To understand the relationships underlying these genetic correlations, we first used GenomicSEM\textsuperscript{16}. GenomicSEM uses structural equation modelling to decompose the genetic covariance matrix, calculated using multivariate LD score regression, of a set of traits. Parameters are estimated by minimizing the difference between the observed genetic covariance matrix and the covariance matrix derived from the model (Supplementary Sect. 8).
We fitted a series of genetic regression models in which AFB (or AFS) was regressed on both years of education and one other possible mediating trait, such as openness, cognitive performance, ADHD and age at initiation of smoking (Supplementary Fig. 12A,B and Supplementary Table 12A–L). In other words, we wanted to test whether the strong genetic correlation of AFS/AFB with education was the result of another mediating trait such as personality, ADHD or substance use. We found that the genetic correlation of years of education with AFB and AFS was independent of factors such as risk tolerance, substance use and psychiatric disorders. This suggests that the genetic correlation between years of education and AFB is largely a product of a strong bi-directional relationship between these traits, rather than being both downstream of a common unidentified cause. The exception was age at initiation of smoking (as noted above, a window into risky adolescent behaviour), which partially mediated the relationship of AFB and AFS with years of education.

EFA was then used to examine whether the genetic signal of the onset of reproductive behaviour originated from two genetically distinguishable subclusters of reproductive biology versus externalising behaviour. Using a two-factor EFA model to fit the genetic covariance matrix of AFS and AFB with these two additional traits, we found that the entire model accounted for 47% of the overall variance, with the majority of variance significantly predicted by externalising factors (0.90 ± 0.04) and age at menarche (0.16 ± 0.03). We note that selection bias, induced by the fact that AFB can only be predicted by externalising factors (0.90 ± 0.04), may have attenuated the effects of AFB. Even when BMI is included in the model, the level of attenuation of educational attainment by AFB remains striking.

The majority of pairs of phenotypes, we found strong evidence of bi-directionality, which was also seen after applying Steiger fitting. The relationship between AFB and years in education appeared to be the explanatory factor that linked AFB to the two risk-taking phenotypes. This was not the case, however, for AFS, where the analysis suggests that age at initiation of smoking (and the environment and processes that lead to this) are upstream of the start of AFS. In that case, the relationship was significant when assessed as age at smoking to AFS but not the other way round. Of note, associations were much stronger for age at smoking initiation than for risk-taking behaviour assessed in adulthood, suggesting that the timing of this behaviour is key.

A second set of MR analyses examined whether AFS and AFB PGs have effects on type 2 diabetes (T2D) and coronary artery disease (CAD). Acknowledging the substantial overlap between the most significant signals for AFB, AFS and education-related phenotypes, we used adjusted models to estimate effects independent of years of education (Fig. 4, Supplementary Table 13B and Supplementary Fig. 16). Given the extent of the overlap, we were also interested to investigate whether AFB or AFS might attenuate any association, particularly with education. T2D and CAD were chosen since they are two common major diseases, with broadly defined behavioural risk factors. Findings show that the association with years of education and later-life diseases are substantially attenuated by the effects of AFB. We also found a strong association of the BMI weights with the AFS SNPs but note that, even when BMI is included in the model, the level of attenuation of the educational attainment results by AFB remains striking. This concurs with a large body of research that has established a biological association with the timing of AFB and metabolic diseases including early AFB linked to high blood pressure, obesity and diabetes. Reproductive timing thus appears to capture a latent variable that detects these metabolic effects and is a marker of a broader socio-behavioural trajectory captured by AFB.

Finally, since we were also interested in infertility-related phenotypes, bi-directional MR was performed with AFS and AFB with polycystic ovarian syndrome (PCOS) and, given the nature of the disease, on women only. Our findings (Supplementary Table 13C) suggest that PCOS leads to later AFB. We find no effect
of PCOS on AFS or of either AFS or AFB to PCOS, suggesting that the causal link is infertility-related with PCOS contributing to later AFB.

**Cox models of a PGS for AFB on longevity.** The disposable soma theory of ageing hypothesizes an evolutionary trade-off between investments in somatic maintenance, such as remaining in education, that in turn reduces resources available for reproduction. To test trade-offs between reproductive behaviour and senescence as argued in the ageing and longevity literature$^{26}$, we conducted Cox proportional hazard models analyses to test whether our AFB PGS was associated with (parental) longevity (Supplementary Table 14). We first estimated a baseline Cox proportional hazard model of our AFB PGS on parental longevity and then included the PGS for educational attainment and risk covariates, followed by a final model including number of siblings as a proxy for parental fertility. We found that a genetically predicted one s.d. increase in the PGS for AFB is associated with a 2–4% reduction in parental mortality at
Fig. 6 | Summary GWAS of timing of onset of reproductive behaviour: AFS and AFB. Summary of GWAS meta-analysis results, highlighting that the timing of onset of reproductive behaviour is shaped by the combined effects of reproductive biology and externalizing behaviour, but also by exogenous environmental factors. Sex-specific genetic correlations are higher for AFB than AFS, with gene prioritization revealing some genes prioritized for men and women as well as sex-specific findings. Of the prioritized genes, 99 were expressed at the protein level in cell types of brain, glands and/or (fe)male reproductive organs. The fact that some prioritised proteins are expressed in some relevant tissues does not provide clear evidence supporting a causal role. Figure created by authors.

any age, suggesting that there is probably a trade-off between the timing of reproduction and longevity.

Gene prioritization. To understand the biology represented by the variants associated with AFS and/or AFB, we performed a gene prioritization analysis that connected variants to genes and prioritized candidate genes based on likely involvement in reproductive biology or psychiatric traits. To this end, we used predicted gene function, single-cell RNA sequencing data in mice28,29, literature mining30, in silico sequencing31 and summary-data based MR (SMR)32 using expression quantitative trait locus (eQTL) data from brain and blood. Integrating results across all approaches resulted in the prioritization of 386 unique genes: 314 genes in 159 loci for AFS and 106 genes in 42 loci for AFB (Supplementary Tables 15A–19C). Of these, 99 were expressed at the protein level in cell types of brain, glands and/or (fe)male reproductive organs (Fig. 5).44 Gene prioritization in sex-specific loci resulted in the prioritization of 11 genes for AFB in women, 1 gene for AFS in women and 23 genes for AFS in men. Of these, 12 genes at three loci were expressed at the protein level in relevant tissues (Supplementary Fig. 17).

Genes that play a role in follicle stimulating hormone (CGA), oocyte development (KLF17) and implantation and placental growth (ESR1, SUMO1, ARNT, CAV1 and E2F1) were prioritized for AFS in data from men and women combined, while FSHB and ESR1 were also prioritized for AFB. Other genes prioritized in loci identified in the pooled meta-analyses were expressed at the protein level in (developing) sperm, highlighting a role for spermatid differentiation (KLF17) for AFS, as well as for sperm morphogenesis and binding between acrosome-reacted sperm and the zona pellucida (ZPB8) for AFB. The meta-analysis in data from only women yielded genes related to endometriosis (CCR1) and spontaneous abortion (CXCR6) for AFB (Supplementary Fig. 19).

Taken together, these results suggest that intrinsic biological processes related to fertility are also related to the onset of sexual behaviour in men and women. Interestingly, NUP210L (prioritized for AFS and highly expressed in developing and mature sperm45) is normally testsis specific but was recently shown to be expressed in prefrontal cortex neurons of G allele carriers in rs114697636 (minor allele frequency of 3%), attributed to allele-specific activation through improved binding affinity for testis receptor 2 (ref. 46). Methylation of, and variants near, NUP210L have been associated with psychological development disorders, intelligence and mathematical ability, illustrating how a testis-specific gene could be linked to brain function in some individuals. We note, however, that the fact that some prioritized proteins are expressed in some relevant tissues does not provide clear evidence supporting a causal role for the prioritized genes.

Several genes prioritized in AFS-associated loci in data from men and women combined have previously been implicated in risk-seeking behaviour, sociability and anxiety (GTF21, TOP2B, E2F1, NCAM1, NFASC52 and MEF2C). In the sex-specific meta-analysis for AFS, a role for externalising behaviour was supported through ERBB4 in women and through SLC44A1 and NR1H3 in men. ERBB4 has previously been linked to fear, anxiety47, schizophrenia55 and PCOS56; SLC44A1 encodes a choline transporter that plays a key role in cerebral inhibition related to substance use and depressive disorders57; and NR1H3 has been implicated in major depressive disorder58. These genes provide concrete examples of how genetic variants associated with externalising behaviour may also associate with the initiation of reproductive behaviour.

The gene prioritization results partly mirror and complement the rigorous post-GWAS in silico association analyses we performed for loci identified for AFS and AFB. However, experimental validation is required before firm conclusions can be drawn about the involvement...
of, and mechanisms through which, prioritized candidate genes influence AFS and AFB. See the further information on protein–protein interaction hubs in Supplementary Fig. 17 and on genes highlighted by literature mining in Supplementary Sect. 11 (ref. 30).

Discussion

We present the results of a GWAS on the onset of human reproductive behaviour as measured by AFS (N = 387,338) and AFB (N = 542,901). We identified 371 signals harbouring at least 386 prioritized candidate genes, using 1000G imputed genotype data and an X-chromosome analysis, which allowed us to detect considerably more signals than before (Fig. 6). In comparison, a recent GWAS for T2D,6, for instance, detected 243 loci. Similar to previous work, we showed that the total SNP heritability accounted for 10–22% of phenotypic variance and varied by birth cohort.12,60 The incremental detected 243 loci. Similar to previous work, we showed that the total lifestyle factors related to obesity, T2D or substance use disorders.

A final glaring limitation is our focus on European-ancestry individ-

ations for disease prevention and behavioural interventions into

that appear to be highly related to self-control, which has impli-

cations for disease prevention and behavioural interventions into

and related complex behaviour. The lack of accessibility of publi-

cation and environmental make-up of the sample.

we acknowledge that social science research has found large differences in the earlier initiation of AFS and AFB by lower socioeconomic status, which often coincides with societal inequality46,47 and the socially (not biologically) constructed categories of race and ethnicity. Socioeconomic differences are examined in this article, but results are only applicable to European-ancestry groups, with a need for further cross-ancestry discovery research.

The Human Reproductive Behaviour Consortium is a collaboration studying GWAS of human reproductive behaviour including AFS, AFB, NEB, childhood and related traits. In some cases, we used summary statistics from our first GWAS of AFB and NEB on discovery cohorts (see Supplementary Note and Supplementary Tables 1–3b).

Phenotypes, genotyping, imputation and meta-analysis. AFS is treated as a continuous measure, with individuals considered as eligible if they had given a valid answer with ages lower than 12 years excluded (Supplementary Note 1.2).

Since AFS has a non-normal distribution, a within-sex inverse rank-normal transformation is required. AFB is also treated as a continuous measure, assessed for those who have ever given birth to a child. Details about participating cohorts, sample inclusion criteria, genotyping and imputation, models used to test for association, X chromosome analysis, quality control filters and diagnostics, and analyses given in the Supplementary Note. A sample-size weighted meta-analysis of quality-controlled cohort-level results was performed using METAL software.48 We performed conditional and joint multiple SNP analyses (COJO) to identify further independent SNPs and sex-specific analyses.

Sex-specific genetic effects. We used LD score heritability estimation22 to estimate the genetic correlation between men and women based on the sex-specific summary statistics from the meta-analysis results. There was a large genetic overlap between the sexes for AFB (0.95) and a somewhat lower overlap for AFS (0.79), suggesting sex-specific effects would be important to examine. To determine whether there was evidence for sex-specific effects, we compared the allelic effects for these SNPs between men and women and derived a P value for heterogeneity23. A multiple testing correction (0.05/242 = 2 × 10^-4) was applied to identify sex-specific associations. We then selected a region of ±1 Mb around these lead SNPs to identify genes that may be represented by these lead SNPs, followed by gene prioritization as we did for the main AFB and AFS analyses.

X chromosome analysis. For AFS, the UK Biobank provided results for between 977,536 and 990,735 variants on the X chromosome after QC (Supplementary Table 8). For AFB, 13 cohorts provided information on the X chromosome. Overall, we received 23 files: 13 for women, 8 for men and 2 for the pooled analysis in case there were individuals who were relatives in the data. On average, 275,023 variants survived QC with a minimum of 99,794 in women from the Wisconsin Longitudinal Study to 988,304 for the women in the UK Biobank sample (see Supplementary Table 7 for full descriptions). Association analyses on the X chromosome were performed using software suggested in the analysis plan (XWAS, SNPtest or BOLT-LMM) using BOLT-LMM for AFS as this was only assessed in the UK Biobank data; for AFB, METAL was used as described above (Supplementary Note 3.5).

Phenotypic and genotypic historical changes. Descriptive analyses and correlations were undertaken using the UK Biobank data to illustrate phenotypic shifts in AFS and AFB by birth cohort, in addition to changes in the spread of the
distribution. Pearson's correlation coefficients were calculated, and correlation graphs illustrate the changing relationship between the two phenotypes over time. Genotypic changes and SNP heritability by birth cohort were quantified in UK Biobank data using GReML. As described earlier, for each phenotype, we used the 'eur_w_ld_chr' population stratification and environment-moderated effects.

Multi-trait analysis of GWAS. Multi-trait analysis of GWAS (MTAG) results were calculated using GWA meta-analysis results of the following related phenotypes: AFS, AFB, NEB and childlessness. Using summary statistics from the pooled GWAS of each of the traits, MTAG uses bivariate LD score regression to account for unobserved sample overlap.

PGS prediction. We performed out-of-sample prediction in two cohorts: Add Health, based in the United States, and UKHLS. We calculated three sets of GWSs with weights based on meta-analysis results excluding the specific cohort from the calculation. First, pruning and thresholding of all SNPs was performed (250 kb window; r² = 0.1) using PRSice. Second, LDpred PGSs with the LD reference were calculated from the same genotyped files, using prior distributions for the causal fraction of SNPs equal to 1 and LDpred weights calculated under Multi-trait analysis of GWAS. Biobank data using GREML as described earlier. For both traits, we ran ordinary least-squares regression models and report the increment r² as a measure of goodness of fit of the model. Confidence intervals are based on 1,000 bootstrapped samples.

Population stratification and environment-moderated effects. To test whether population stratification biased our results or led to false positives, we used the LD score regression method. For each phenotype, we used the 'eur_w_ld_chr' files of LD scores. These LD scores were computed with genotypes from the European-ancestry samples in the 1000 Genomes Project using only HapMap3 SNPs with MAF > 0.01. We then ran survival models to account for right censoring, which occurs when an individual does not experience the event of first sex or birth by the time of the interview. Using Add Health data, we estimated nonparametric hazard functions based on Nelson–Aalen estimates and then compared individuals in the top and bottom 5% of the PGS and plotted the estimated hazards. To further explore the relationship of environmentally moderated parental genetic effects on our PGSs, we examined PGS prediction across low (0–10%), medium (50–60%) and high (90–100%) PGS percentiles by parents' education status (college versus no college), which serves as a proxy for childhood socioeconomic status.

Genetic correlations. Genetic correlation (r) values were computed to estimate the genetic correlation between the two traits using all polygenic effects captured by the SNPs and LD score regression. We used summary statistics and the 1000 Genomes reference set, and restricted the analysis to European populations. We also followed the common convention of restricting our analyses to SNPs with MAF > 0.01, thus ensuring that all analyses were performed using a set of SNPs that were imputed with reasonable accuracy across all cohorts. The s.e. values were produced by the LDSC python software package that uses a block jackknife over the SNPs. We estimated the genetic correlation between 28 different traits, pooled by both sexes and then divided by sex. Traits were divided into the six categories of reproductive, behavioural, psychiatric disorders, substance use disorders, personality and anthropometric.

GenomicSEM and EFA. In an attempt to understand the aetiology of the correlations, we used the R package GenomicSEM to fit genetic multivariable regression models. GenomicSEM uses structural equation modelling to decompose the genetic covariance matrix, calculated using multivariate LD score regression, of a set of traits. Formally, structural equation models subsume many statistical methods and are quite flexible. We fitted a series of genetic multivariable regression models, in which AFB was regressed on educational attainment (EA) and a trait X, in which we modelled various relevant traits such as openness, cognitive performance and age at smoking (AJ). We also fitted an analogous series of models in which AFS was regressed on EA.

EFA and GenomicSEM by reproductive biology and externalising behaviour. EFA was used to examine whether the genetic signal of the onset of reproductive behaviour originated from two genetically distinguishable subclusters of a biological component and an externalising behaviour component. This would suggest distinct causal mechanisms and subtypes of individuals. We tested this by fitting a two-factor EFA model to the genetic covariance matrix of AFB, AFS, NEB and the three sexes angle (biological component) and risk tolerance (externalising behaviour). To test this further, we estimated more robust and additional measures of reproductive biology and externalising behaviour and a sex-specific analysis of AFB for women. We fitted a GenomicSEM where AFB in women is regressed on age at menopause, age at menarche and a latent factor representing the common genetic tendency to externalising behaviour. The factor is measured by AFS in women, age at initiation of smoking, age first used oral contraception and ADHD, with the model scaled to unit variance for the latent factor. We then tested whether causal pathways linking these phenotypes are potentially bi-directional and whether our phenotypes might offer distinct contributions. We identified 1000 Genomes proxies for our SNPs and used these in multivariate MR models. All data were assumed to be on the forward strand, and because many of these datasets included UK Biobank, allele identifiers were matched to this study as a reference. First, we modelled the interplay between AFB, AFS and EA as well as risk taking (measured in adulthood) and AJ. In each case, inverse-variance weighted and MR-Egger methods were performed with an additional test of inverse-variance weighted once a Steiger filter had been applied to remove SNPs that appeared to show a primary association with the outcome rather than the exposure. Multivariate MR was used to try to dissect causal pathways. A second set of MR analyses focused on links to late-life diseases, namely T2D and CAD, using the same methods. Acknowledging the substantial overlap between the most significant signals for AFB and educational-related phenotypes, we used measurement methods to test whether AFS or AFB had independent effects once the well-established links to length of educational attainment, and BMI were controlled for. Finally, as there was a particular interest in infertility-related phenotypes, bi-directional MR was performed with AFS and AFB and PCOS. In this case, given the sex-specific nature of the disease, a specific analysis was also performed on women only.

Cox models of AFB PGS on longevity. To test trade-offs between reproductive behaviour and senescence, we conducted additional analyses to test whether our PGS for AFB was predictive of (parental) longevity. We restricted our models to mortality after age 60 to limit the possibility that early mortality affects parental fertility (that is, collider bias). We calculated 0.01. We then ran survival models to account for right censoring, which occurs when an individual does not experience the event of first sex or birth by the time of the interview. Using Add Health data, we estimated nonparametric hazard functions based on Nelson–Aalen estimates and then compared individuals in the top and bottom 5% of the PGS and plotted the estimated hazards. To further explore the relationship of environmentally moderated parental genetic effects on our PGSs, we examined PGS prediction across low (0–10%), medium (50–60%) and high (90–100%) PGS percentiles by parents' education status (college versus no college), which serves as a proxy for childhood socioeconomic status.

Gene prioritization. We prioritized candidate genes in pooled and sex-specific GWAS-identified loci using predicted gene functions, single-cell RNA sequencing data in mice and published literature on the anatomical location of the gene, as well as on its functional role. We used in silico sequencing to identify non-synonymous variants with potential functional impact. We prioritized candidate genes in pooled and sex-specific GWAS-identified loci using predicted gene functions, single-cell RNA sequencing data in mice and published literature on the anatomical location of the gene, as well as on its functional role.
We integrated findings across all approaches and retained genes in loci that reached genome-wide significance and that were located within 1 Mb of a GWAS lead SNP. We next used data from the Human Protein Atlas to identify genes amongst 387 genes that are expressed at a low, medium or high protein level in brain, glands and/or reproductive organs at a ‘supported’ or ‘enhanced’ degree of reliability. For the 97 genes that fulfilled these criteria, we mapped the brain, glandular and reproductive cell types in which they are highly expressed at the protein level; used a text-mining approach to extract functions from entries in Intrez, GeneCards and Uniprot and identified phenotypes in mutant mice from the Mouse Genome Informatics database.

**Data availability**

Our policy is to make genome-wide summary statistics widely and publically available. Upon publication, summary statistics will be available on the GWAS catalogue website: https://www.ebi.ac.uk/gwas/downloads/summary-statistics. The phenotype and genotype data for separate studies used in this GWAS are available upon application to each of the participating cohorts, who can be contacted directly to follow their different data access policies. Access to the UK Biobank is available through application with information available at: http://www.ukbiobank.ac.uk.

**Code availability**

No custom code was used, with all analyses and modelling using standard software as described in the Methods section and in detail in the Supplementary Information.

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Reporting Summary

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

- The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
- A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- The statistical test(s) used AND whether they are one- or two-sided
- A description of all covariates tested
- A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
- A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
- For null hypothesis testing, the test statistic (e.g. $F$, $t$, $r$) with confidence intervals, effect sizes, degrees of freedom and $P$ value noted Give $P$ values as exact values whenever suitable.
- For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
- For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
- Estimates of effect sizes (e.g. Cohen’s $d$, Pearson’s $r$), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

**Data collection**
Access to individual level data from from the 36 cohorts used in this GWAS can be obtained by bona fide scientists through application to the specific data providers, with information about each study listed in detail in the Supplementary Note.

**Data analysis**
Upon publication, GWAS summary statistics will be made available at the GWAS Catalog (www.ebi.ac.uk/gwas/downloads/summary-statistics). Analytical methods are described in the Online Methods section and in more detail in the Supplementary Note. Standard software with available code and algorithms was used, namely: METAL, XWAS, SNPtest, BOLT-LMM, GCTA, MTAG, PRSice, LDPred, GenomicSEM, MR-EGGER, and various libraries in R for additional regression analyses and visualization (Exploratory Factor Analysis, Cox Survival Model, ggplot2). For the biological annotation, we used DEPICT, CELLECT (RNAseq data from mouse brain, Tabula muris RNAseq data), Phenolyzer, In silico sequencing, SMR (summary based Mendelian Randomisation), HEIDI, eQTL data.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Upon publication, GWAS summary statistics will be made available at the GWAS Catalog (www.ebi.ac.uk/gwas/downloads/summary-statistics). Access to individual level data from the multiple sources used in this GWAS can be obtained by bona fide scientists through application to each specific data providers, with each data source described in the Supplementary Note.
Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

**Sample size**

Age at first sex (AFS), N=387,338; Age at first birth (AFB), N=542,901

**Data exclusions**

Individuals - both females and males - were eligible for inclusion in analyses if they met the following conditions: a) were assessed for AFS and have had sexual intercourse, for AFB and have given birth to a child (parous), b) all relevant covariates (year of birth) available for individual, c) they were successfully genotyped genome-wide (recommended ≥95%), d) passed the cohort-specific standard quality controls and f) were of European Ancestry. Data exclusions were specified in advance in the analysis plan pre-deposited in the Open Science Framework website: https://osf.io/b4r4b/ European ancestry samples were chosen due to availability of large samples and for no biological or substantive reason. In the Online Methods and Supp Note we acknowledge that (nongenetic) research has found differences in the initiation of AFS/AFB by socioeconomic differences and the social category of ethnicity/race.

**Replication**

Study involves large discovery sample with GWAS summary statistics available at the GWAS Catalog upon publication (www.ebi.ac.uk/gwas/downloads/summary-statistics). Out of sample prediction also conducted & reported in Main paper and Supp Note.

**Randomization**

Participants not allocated into randomized groups. Analysts ran linear regression on AFB and a transformed AFS variable. Since AFS has a non-normal distribution, we asked analysts for a within-sex inverse rank normal transformation. Analysts were asked to include birth year of the respondent (represented by birth year – 1900/10), its square and cubic to control for non-linear birth cohort effects. For those with family-based data, we suggested controlling for non-independence of family members or only include one family member in the analyses. We furthermore asked studies with family data to run a pooled GWAS on both sexes. Combined analyses that included both men and women also needed to include interactions of birth year and its polynomials with sex. In general, we asked to include top principal components to control for population stratification and cohort specific covariates if appropriate. Some cohorts only used birth year and not its polynomials because of multi-collinearity issues/convergence of the GWA analysis. Omission of these nonlinear birth year effects is unlikely to lead to biased inferences, since genotypes are not usually considered to be truly associated with birth year. However, inferences might be less accurate (i.e., have larger standard errors), since omission of nonlinear birth year effects can lead to larger residual variation.

**Blinding**

This was a GWAS and blinding was therefore not relevant.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a | Involved in the study |
|-----|-----------------------|
| ☒ | Antibodies |
| ☒ | Eukaryotic cell lines |
| ☒ | Palaeontology |
| ☒ | Animals and other organisms |
| ☒ | Human research participants |
| ☒ | Clinical data |

### Methods

| n/a | Involved in the study |
|-----|-----------------------|
| ☒ | ChiP-seq |
| ☒ | Flow cytometry |
| ☒ | MRI-based neuroimaging |

Human research participants

| Policy information about: | studies involving human research participants |
|--------------------------|-----------------------------------------------|
| Population characteristics | Both males and females of European ancestry if they were assessed for AFS and have had sexual intercourse and assessed for AFB and have given birth to a child. |
| Recruitment | Recruitment varied over the 36 studies, but it is acknowledged in the main text and Supp Note that often samples used for GWAS may suffer from ascertainment bias. We also conducted additional analyses such as how polygenic score predictions differ by childhood socioeconomic status (main paper and Supp Note). |
| Ethics oversight | Ethics was approved by the University of Oxford but also for each individual data source locally. |
Note that full information on the approval of the study protocol must also be provided in the manuscript.