Genome-wide analysis identifies 12 loci influencing human reproductive behavior

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Abstract

The genetic architecture of human reproductive behavior – age at first birth (AFB) and number of children ever born (NEB) – has a strong relationship with fitness, human development, infertility and risk of neuropsychiatric disorders. However, very few genetic loci have been identified and the underlying mechanisms of AFB and NEB are poorly understood. We report the largest genome-wide association study to date of both sexes including 251,151 individuals for AFB and 343,072 for NEB. We identified 12 independent loci that are significantly associated with AFB and/or NEB in a SNP-based genome-wide association study, and four additional loci in a gene-based effort. These loci harbor genes that are likely to play a role – either directly or by affecting non-local gene expression – in human reproduction and infertility, thereby increasing our understanding of these complex traits.

Introduction

Human reproductive behavior – age at first birth (AFB) and number of children ever born (NEB) – has been associated with human development,[1,2] infertility[3,4] and neuropsychiatric disorders[5]. Reproductive tempo (AFB) and quantum (NEB) are cross-cutting topics in the medical, biological, evolutionary and social sciences and central in national and international policies.[6] Advanced societies experienced a rapid postponement of AFB, with the mean AFB of women now being 28-29 years in many countries.[7] This increase in AFB has been linked to lower fertility rates, unprecedented childlessness (~20%) and infertility, which affects 10 to 15 % of couples.[8] An estimated 48.5 million

couples worldwide are infertile, with a large part of subfertility, particularly in men, remaining unexplained.[9] Although infertility has been related to advanced AFB, ovulation defects, spermatogenic failure, and single- or polygenic defects, their causal effects remain unsubstantiated.[10]

Until now, genetic and clinical research has focussed on proximal infertility phenotypes.[3,4,10,11] AFB and NEB represent accurate measures of complex reproductive outcomes, are frequently recorded and consistently measured, and are key parameters for demographic population forecasting.[12] There is evidence of a genetic component underlying reproduction, with heritability estimates of up to 50% for AFB and NEB (Supplementary Figure 1).[6] A recent study attributed 15% of the variance of AFB and 10% of NEB to common genetic variants.[13] There are also sex-specific differences in human reproduction, related to the timing of fertility, fecundability and sex-genotype interactions (Supplementary Note). Researchers have given less attention to traits such as NEB due to an erroneous and frequently repeated misinterpretation of Fisher's[14] Fundamental Theorem of Natural Selection that the additive genetic variance in fitness should be close to zero. The misreading had a naively intuitive appeal: genes that reduce fitness should have been less frequently passed on. Fisher, however, actually argues that fitness is moderately heritable in human populations (for a discussion see the Supplementary Note). Since no established genes are currently available for clinical testing of infertility,[10] isolating genetic loci and their causative effects has the potential to provide new insights into the etiology of reproductive diseases and novel diagnostic and clinical technologies for infertility treatment.

RESULTS

We report the largest meta-analysis of genome-wide association studies (GWAS) to date of 251,151 individuals for AFB and 343,072 for NEB from a total of 62 cohorts of European ancestry. We identify 12 independent loci (10 of which are novel and 2 previously identified in a study on age at first sexual intercourse[11]) that are significantly associated with AFB and/or NEB in men, women and/or both sexes combined (Table 1). Follow-up analyses identified a number of genetic variants and genes that likely drive GWAS associations. We also quantified the genetic overlap with biologically adjacent reproductive, developmental, neuropsychiatric and behavioral phenotypes. A detailed description of all materials and methods is available in the **Supplementary Note.**

Meta-analysis of GWAS

Associations of AFB (mean ± SD 26.8±4.78 years) and/or NEB (mean ± SD 2.3±1.43 children) with NCBI build 37 HapMap Phase 2 imputed SNPs were examined in 62 cohorts using multiple linear regression under an additive model, in men and women separately (Supplementary Note). Associations were adjusted for principal components – to reduce confounding by population stratification[15] – as well as for the birth year of the respondent and its square and cubic to control for

non-linear birth cohort effects (Supplementary Note and Supplementary Tables 1-,2). NEB was assessed only for those who had completed their reproductive period (age ≥ 45 women; age ≥ 55 men), while AFB was only assessed for those who were parous. Quality control (QC) was conducted in two independent centers using QCGWAS[16] and EasyQC[17] (Supplementary Note). Results were subsequently meta-analyzed for the 2.4M SNPs that passed QC filters (Supplementary Note) and reported for men and women combined and separately.

We applied a single genomic control at the cohort level and meta-analyzed results using a sample-size weighted fixed effect method in METAL (Supplementary Note). The PLINK clumping function isolated 'lead SNPs' – i.e. those with the lowest *P*-value for association that are independently associated – using an r^2 threshold of 0.1 and distance threshold of 500 kb. For AFB, we identified ten genome-wide significantly associated loci (i.e., $P<5x10^{-8}$ for combined and $P<1.67x10^{-8}$ for sex-specific results adjusted for multiple testing) of which nine were significantly associated in both sexes combined and one in women only (N=154,839) (Figure 1a, Table 1). Three loci were significantly associated with NEB: two in both sexes combined and one in men only (N=103,736) (Figure 1b, Table 1, Supplementary Note). One locus on Chr 1 reached significance for association with both AFB and NEB with an r^2 of 0.57 between the two lead SNPs, suggesting a shared genetic basis for the two traits (Table 2). A statistical test of sex-specific effects confirms that differences are mainly due to variation in sample size and not variation in effect sizes (Supplementary Note).

As for other complex traits[18], the Q-Q plots of the meta-analyses exhibit strong inflation of low *P*-values (Figure 2), suggesting that although cohorts controlled for the top principal components and cohort-level genomic control was applied (Supplementary Note), residual population stratification may remain. However, the LD Score intercept method[19] as well as a series of individual and within-family regression analyses using polygenic scores as predictors[20,21] (Supplementary Note) indicated that the observed inflation is almost entirely attributable to a true polygenic signal, rather than population stratification.

Gene-based GWAS

To increase the power to find statistically significant associations and causal genes, we additionally performed a gene-based GWAS using VEGAS.[22,23] The results confirmed top hits from the single-SNP analyses. For AFB, seven loci from the SNP-based GWAS were also represented in the gene-based analysis (Supplementary Table 3), and three additional loci emerged, represented by *SLF2* (Chr 10), *ENO4* (Chr 10) and *TRAF3-AMN* (Chr 14). For NEB, one locus from the SNP-based GWAS was represented in the gene-based analysis – i.e. *GATAD2B* (Chr 1) – and one novel locus on Chr 17 was identified (Supplementary Table 4).

Causal variants

To identify functional and potentially causal variants – coding or regulatory – within loci identified in the SNP-based GWAS (Table 1), we first performed an *in silico* sequencing annotation analysis using the post-GWAS pipeline reported by Vaez *et al*.[24] This showed that rs10908557 on Chr 1 is in high LD with non-synonymous SNPs in *CRTC2* (rs11264680; r^2=0.98) and *CREB3L4* (rs11264743; r^2=0.94) (see Causal genes, Supplementary Table 5). Interestingly, rs11264743 is considered 'deleterious' and 'probably damaging' by SIFT and PolyPhen, respectively (Ensembl release 83). In addition, rs2777888 on Chr 3 is in high LD with two non-synonymous SNPs in *MST1R* (rs2230590; r^2=0.95 and rs1062633; r^2=0.95) (Table 1, Supplementary Table 5).

We subsequently performed a comprehensive analysis using results from the ENCODE[25] and RoadMap Epigenomics[26] projects as integrated in RegulomeDB,[27] to identify variants that likely influence downstream gene expression via regulatory pathways. Amongst all SNPs that reached $P<5x10^{-8}$ in the meta-analyses (N=322), 50 SNPs in five loci show the most evidence of having functional consequences (Table 1, Supplementary Table 6). Two sets of SNPs on Chr 1 (18 SNPs) and Chr 3 (25 SNPs) particularly stand out. The most promising SNP in the Chr 1 locus (rs6680140) is located in an H3K27ac mark, often found near active regulatory elements, and lies in a DNaseI hypersensitivity cluster where eight proteins are anticipated to bind. One of these proteins is cAMP responsive element binding (CREB) binding protein, encoded by *CREBBP* (see Causal genes). In the Chr 3 locus, rs2526397 is located in a transcription factor-binding site and is an eQTL for *HYAL3* in monocytes, while rs2247510 and rs1800688 are located in H3K27ac sites and DNaseI hypersensitivity clusters where a large number of transcription factors are expected to bind (see Causal genes, Supplementary Table 6). An analysis using Haplotter showed that rs2247510 and rs7628058 in the Chr 3 locus are amongst the 5% of signals that show most evidence of positive selection in the population. The same applies to the lead SNP of the Chr 14 locus for NEB (rs2415984).

Causal genes

Information on the function and anticipated relevance of genes in the 12 loci identified in the SNP-based GWAS that are most likely to be causal based on all evidence discussed below is provided in Table 2.

***Cis* and *trans* eQTL and meQTL analyses**

Identifying alterations in gene methylation status and/or expression levels in relation to GWAS-identified variants may help prioritize causal genes. We examined associations with gene expression and methylation status for the 12 independent lead SNPs in whole-blood BIOS expression (e)QTL (N=2,116) and methylation (me)QTL databases in *cis* and *trans* (N=3,841). [28,29] Seven SNPs were associated with gene expression in *cis* of 54 unique genes (Table 1, Supplementary Table 7). Five of

the seven SNPs were in high LD (r^2>0.8) with the strongest eQTL of at least one of the genes within the corresponding loci, indicating that the SNP associated with AFB or NEB and the SNP most significantly associated with expression tag the same functional site, i.e., rs10908557 (associated with the expression of *CRTC2* and *SLC39A1*), rs1160544 (*AFF3*), rs2777888 (*RBM6*, *RNF123* and *RBM5*), rs2721195 (*CYHR1*, *GPT*, *RECQL4* and *PPP1R16A*) and rs293566 (*NOL4L*). Three SNPs were associated with the expression of a total of eight genes in *trans* (Table 1, Supplementary Table 8). Of these SNPs, only rs2777888 was in high LD (r^2>0.8) with the strongest eQTL for three of its five associated genes: *LRFN1*, *LAMP2* and *FGD3*.

The meQTL analysis showed that 11 of the 12 independent lead SNPs were associated with DNA methylation of a total of 131 unique genes in *cis* (Table 1, Supplementary Table 9). Seven of the 11 SNPs were in high LD (r^2>0.8) with the strongest meQTL of one of the corresponding methylation sites, i.e., rs10908557 (associated with methylation of *CRTC2, SLC39A1, CREB3L4, DENND4B* and *RAB13*), rs1160544 (*AFF3*), rs2777888 (*CAMKV*), rs6885307 (*C5orf34*), rs10056247 (*JADE2*), rs2721195 (*CYHR1*) and rs13161115 (*EFNA5*). Three of the SNPs were associated with the same genes for both methylation and gene expression in *cis*: rs10908557 (*CRTC2*), rs1160544 (*AFF3*) and rs2721195 (*CYHR1*) (Supplementary Tables 7,9). Three SNPs were associated with methylation of a total of ten genes in *trans* (Table 1, Supplementary Table 10). Of these SNPs, only rs2777888 was in high LD (r^2>0.8) with the strongest meQTL of a corresponding methylation site (*ASAP3*). Of note: rs2777888 was also a *trans* eQTL.

Gene prioritization

We used four publicly available bioinformatics tools to systematically identify genes that are more likely than neighboring genes to cause the associations identified by our GWAS. Of all genes that reached P<0.05 in analyses using Endeavour,[30] MetaRanker[31] and ToppGene,[32] eight genes were prioritized for both AFB and NEB: *TPM3*, *GRM7*, *TKT*, *MAGI2*, *PTPRD*, *PTPRM*, *RORA* and *WT1*. Data-driven Expression-Prioritized Integration for Complex Traits (DEPICT) – a fourth, comprehensive and unbiased recently described gene prioritization tool[33] – identified three genes in GWAS significant loci as likely being causal for AFB (*MON1A*, *RBM6* and *U73166.2*) (Supplementary Tables 11, 12).

Gene-based results from RegulomeDB

An analysis using RegulomeDB identified 50 SNPs in five loci that most likely have regulatory consequences (see Causal variants, Supplementary Table 6). Eighteen and 25 of these SNPs are within the Chr 1 and Chr 3 loci, respectively. Amongst the genes that – at a protein level – bind at the site of one or more of the 18 variants in the locus on Chr 1 are *CREBBP*, *HNF4A*, *CDX2* and *ERG*. These genes may act upstream in the causal pathway and influence the expression of causal genes at

this locus. Of the 25 SNPs on Chr 3, ten were eQTLs for *RBM6* in monocytes, and seven were eQTLs for *HYAL3* in monocytes. Amongst the genes that – at a protein level – bind at rs2247510 and rs1800688 in the Chr 3 locus are *ARID3A*, *REST* and *TFAP2C*, as well as *HNF4A* and *CDX2*, which also bind at the Chr 1 locus.

Five genes encode proteins that bind at the site of both SNPs on Chr 2 that reach $P<5x10^{-8}$ in the meta-analysis of GWAS. One of these is *REST* (see Chr 3 locus), another one – *ESR1* – is the most likely causal gene in the Chr 6 locus.

Functional network and enrichment analyses

Functional network analysis using five prioritized candidate gene sets as input (Supplementary Note) showed no significantly enriched biological function. No biological function was significantly enriched after correction for multiple testing using the Benjamini-Hochberg procedure. Similarly, no reconstituted gene sets and cell or tissue types were significantly enriched in the GWAS meta-analysis results based on results from the DEPICT analysis (Supplementary Tables 13-20). The lack of significantly enriched genes, tissue sets and biological functions reflects the need for a larger sample size but also the distal nature of the phenotypes, which are influenced by a mixture of biological, psychological and socio-environmental factors.

Polygenic prediction

To assess the predictive power of our results, we produced polygenic scores for AFB and NEB using sets of SNPs whose nominal *P*-values ranged from $P<5x10^{-8}$ (i.e. using only genome-wide significant SNPs) to 1 (using all SNPs that passed quality control) using PRSice[34] (Supplementary Note). We then performed a series of four different out-of-sample predictions in four independent cohorts: HRS, Lifelines, STR and TwinsUK. Across the four cohorts, the mean predictive power of a polygenic score constructed from all measured SNPs is 0.9% for AFB and 0.2% for NEB (Supplementary Figure 2). Despite the low predictive power of the polygenic scores, the results showed that a 1 standard deviation (SD) increase of the NEB polygenic score is associated with a 9% (95% CI 5%–13%) decrease in the probability for women to remain childless, with no significant association in men (Supplementary Table 21). When we control for right-censored data using a survival model for AFB, we found that a 1SD increase in the AFB polygenic score is associated with an 8% (95% CI 7%–10%) reduction in the hazard ratio of reproduction in women and 3% (95% CI 1%–5%) in men (Supplementary Table 22). As an additional test, we examined whether the aforementioned polygenic scores for AFB and NEB can predict related fertility traits such as age at menopause and age at menarche (Supplementary Table 23). Our estimates indicate that a 1SD increase of the AFB polygenic score is associated with a 3% decrease in age at natural menopause (95% CI 1%–5%) and a 20 day increase in age at menarche (95% CI 0.4–40 days).

Genetic association with related traits and diseases

Several loci for which the associations with AFB and NEB reach genome-wide significance are associated with behavioral and reproductive phenotypes. The lead SNPs in the Chr 2 and Chr 3 loci have been associated with educational attainment[35] and the locus on Chr 5 with age at menarche[36] while the locus on Chr 6 has recently been associated with age at first sexual intercourse[37] (Supplementary Table 24). Some of the 38 loci for age at first sexual intercourse that were recently identified in 125,667 UK Biobank participants were also associated with AFB (in/near *RBM6–SEMA3F* and *ESR1*) and NEB (in/near *CADM2* and *ESR1*). The lead SNPs for *RBM6–SEMA3F* (rs2188151) and *ESR1* (rs67229052) are in LD with our lead SNPs for AFB on Chr 3 (r^2= 0.44) and Chr 6 (r^2=0.94), respectively. An *in silico* pleiotropy analysis showed that our lead SNP in the Chr 3 locus (rs2777888) is in LD (r^2=0.59) with rs6762477 – which has been associated with age at menarche[2] – while other SNPs in the same locus have been associated with HDL cholesterol[38] (rs2013208; r^2=0.81) and BMI[39] (rs7613875; r^2=0.81) (Supplementary Table 5). We next performed an exploratory analysis using the proxy-phenotype method[40] to examine if the SNPs strongly associated with AFB in women are empirically plausible candidate SNPs for related traits like age at menarche and age at menopause (Supplementary Note). After controlling for multiple testing, we identified three AFB-associated SNPs near rs2777888 on Chr 3 (rs9589, rs6803222 and rs9858889) that are also associated with age at menarche (P<4.10x10^{-4}). None of the AFB or NEB-associated SNPs are associated with age at menopause.

We performed a bivariate LD score regression analysis[41] to estimate the pairwise genetic correlation with 27 publicly available GWAS results for traits associated with human reproductive behavior (Supplementary Note). AFB shows significant and positive genetic correlations with the human (reproductive) developmental traits age at menarche, voice breaking, age at menopause, birth weight and age at first sexual intercourse, as well as with years of education. Conversely, having more AFB-increasing alleles is associated with a lower genetic risk of smoking (ever, number of cigarettes, later onset) and with lower insulin resistance-related phenotypes, i.e. BMI, waist-hip-ratio adjusted for BMI, fasting insulin, triglyceride levels and risk of diabetes (Figure 3 and Supplementary Table 25). All genetic correlations remain significant after Bonferroni correction for multiple testing (P<2.6x10^{-3}). Years of education (P=6.6x10^{-14}) and age at first sexual intercourse (P=1.14x10^{-15}) are the only traits that show significant and negative genetic correlations with NEB. We also observed significant genetic correlations of r_g=0.86 (SE=0.052) for AFB and r_g=0.97 (SE=0.095) for NEB between men and women, implying that most genetic effects on reproductive behavior resulting from common SNPs are shared across the sexes.

Discussion

This GWAS is the largest genetic epidemiological discovery effort for human reproduction to date, with critical implications for population fitness and clear physiological mechanisms linking hypothesized genes and observed phenotypes. Related studies previously focussed on reproductive life span[42,43], age at first sexual intercourse[11] and more proximal infertility phenotypes,[2–4] largely overlooking AFB and NEB. The rapid postponement of AFB and increased infertility and involuntary childlessness in many societies[7] makes it important to uncover the genetic and biological architecture of reproduction. We identify ten novel and confirm two recently identified genetic loci that are robustly associated with AFB and NEB, as well as variants and genes within these loci that likely drive these associations. Four additional loci were identified in a gene-based GWAS.

Two loci that show interesting results in follow-up analyses are located on Chrs 1 and 3. The lead SNPs of the Chr 1 locus for AFB and NEB are in LD with likely functional non-synonymous SNPs in genes encoding: 1) CREB (cAMP responsive element binding) regulated transcription co-activator 2 (*CRTC2*), which at a protein level acts as a critical signal mediator in follicle-stimulating hormone (FSH) and transforming growth factor β1(TGFβ1)-stimulated steroidogenesis in ovarian granulosa cells[44]; and 2) CREB protein 3-like 4 (*CREB3L4*),[45] which in humans is highly expressed in the prostate, ovaries, uterus, placenta and testis, and plays a role in spermatid differentiation[46] and male germ cell development.[47] The lead SNP and/or functional variants in LD with it are also associated with the methylation status of these two genes and expression of *CRTC2* in whole blood and lymphocytes. Three promising functional variants in the Chr 1 locus reside in binding sites of the transcriptional co-activator CREB binding protein (CREBBP). In addition to a direct effect of the above-mentioned non-synonymous SNPs on protein function, the associations of AFB and NEB with variants in the locus on Chr 1 may thus be mediated by alterations in cAMP responsive element binding in men and women. The locus on Chr 1 also harbours *DENND4B*, a paralogue of *DENND1A*, implicated in PCOS.[48] While *DENND1A* is expressed at the protein level in the ovary and testis, DENND4B is in the cervix, and its function and role are less well understood.

The lead SNP of the locus on Chr 3 (rs2777888) is associated with methylation and expression of several genes – in *cis* and *trans* – that are known to play a role in cell cycle progression and/or sperm function. First, rs2777888 is associated with the expression of *RNF123* (or *KPC1*) in *cis*, which plays a role in cellular transition from the quiescence to proliferative state. Secondly, rs2777888 – or functional variants in LD with it – may influence the cell cycle by altering the expression of *RBM5* and *RBM6* (RNA binding motif proteins 5 and 6). The former plays a role in cell cycle arrest and apoptosis induction and regulates haploid male germ cell pre-mRNA splicing and fertility in mice. *RMB5* mutant mice exhibit spermatid differentiation arrest, germ cell sloughing and apoptosis, leading to lack of sperm in ejaculation.[49] Thirdly, rs2777888 affects expression of *LAMP2* in *trans*, which is located on the X chromosome and encodes a lysosomal membrane protein involved in the

acrosome reaction, i.e. the enzymatic drill allowing sperm to penetrate and fertilize ovum.[50] *LAMP2* is expressed at the protein level in male and female reproductive organs with an effect size of rs2777888 for *LAMP2* mRNA expression that is almost twice as large in women than in men (Supplementary Figure 4). This suggests an important role for the lysosome in both sperm and ovum. Finally, functional variants in the Chr 3 locus are associated with the mRNA expression of *HYAL3* in monocytes (hyaluronoglucosaminidase 3). The latter degrades hyaluronan, which also plays an important role in sperm function and the acrosome reaction.[49,51]

Functional follow-up experiments could disentangle the potential interplay between many candidate genes in the loci on Chrs 1 and 3 on reproductive behavior and – given our *in silico* results – infertility. This can be extended to candidate genes in the remaining loci identified in the present study, some of which are relevant for fertility: mice lacking *EFNA5* (Chr 5 NEB locus) are subfertile,[52] *ESR1* on Chr 6 encodes an estrogen receptor, [53,54] and *CYHR1* on Chr 8 is involved in spermatogenesis[55]. Such experiments would help understand whether binding of estrogen receptor 1 – encoded by *ESR1* in the locus on Chr 6 – at the site of functional variants in the locus on Chr 2 drives or mediates the association with AFB in the Chr 2 locus, as well as to identify and characterize causal genes. Recent developments in high-throughput, multiplex mutagenesis using Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) and associated systems (Cas9) allow such experiments to be performed using *in vivo* model systems.[56]

AFB and NEB are not only driven by biological processes, but are also subject to individual choice and personal characteristics – such as personality traits – as well as by the historical, cultural, economic and social environment (e.g., effective contraception, childcare availability). Demographic research has shown a strong positive association between AFB and educational attainment.[12] We show that the associations between fecundity, reproductive behavior and educational attainment are partly driven by genetic factors, and identified loci that are associated with AFB as well as with e.g., age at first sexual intercourse [37] and educational attainment.[35]

Our findings are anticipated to lead to insights into how postponing reproduction may be more detrimental for some – based on their genetic make-up – than others, fuel experiments to determine 'how late can you wait'[57] and stimulate reproductive awareness. Causal genes in the loci we identified may serve as novel drug targets, to prevent or delay age-related declines in fertility and sperm quality, or increase Assisted Reproductive Technology efficiency. Our study is the first to examine the genetics of reproductive behavior in both men and women, and the first that is adequately powered to identify loci both in women and men. We also provide support for Fisher's theorem that fitness is moderately heritable in human populations. While effect sizes of the identified common variants are small, there are examples of GWAS-identified loci of a small effect that end up leading to important biological insights.[58,59] Many of our findings suggest a role for sperm quality, which is one lead for

researchers to pursue. Since current sperm tests remain rudimentary, our findings could serve as a basis for 'good quality' sperm markers. We identified variants that are likely causal – both coding and regulatory – as well as a set of genes that likely underlie the associations we identified. Follow-up experiments in animal models are required to confirm and characterize the causal genes in these loci.

URLs

Analysis plan pre-deposited in the Open Science Framework website: https://osf.io/53tea/
Gene Network: http://129.125.135.180:8080/GeneNetwork/
Reprogen Website: http://www.reprogen.org/data_download.html
Sociogenome website: http://www.sociogenome.com
Social Science Genetic Association Website: http://thessgac.org

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AUTHOR CONTRIBUTIONS

Senior investigators who led writing, analysis, study design M.C.M, H.S, M.d.H.; Senior investigators participated in study design: P.K., D.B., D.C., Junior investigator who contributed to the study design and management: N.B.; Population stratification: N.B. and F.C.T.; Genetic correlations and polygenic scores prediction: N.B.; Meta-analysis and quality control: N.B., R.dV., J.M., I.M.N.; Biological annotation: R.J., M.d.H., A.V.; Sex-specific genetic effects: F.T.; Bivariate and Conditional analysis

of the two fertility traits: X.S., J.F.W., D.I.C.; Gene-based analysis V.T., S.W.v.d.L. Authors not listed contributed to recruitment, genotyping, or data processing for the meta-analysis. Results can be downloaded from the SOCIOGENOME (http://www.sociogenome.com) and SSGAC website (http://www.thessgac.org/). Data come from multiple studies, most of which are subject to a MTA, and are listed in the Supplementary Information. Correspondence and requests for materials should be addressed to the corresponding authors or info@sociogenome.com.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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Figure 1. Manhattan plots of SNPs for AFB (age at first birth) and NEB (number of children ever born) in single genomic control meta-analysis. SNPs are plotted on the x-axis according to their position on each chromosome against association with AFB (panel a) and NEB (panel b). The solid blue line indicates the threshold for genome-wide significance ($P<5x10^{-08}$) and the red line, the threshold for suggestive hits ($P<5x10^{-06}$). Blue points indicate SNPs in a ±100 KB region around genome-wide significant hits. Gene labels are annotated as the nearby genes to the significant SNPs.

Figure 2. Quantile-quantile plots of SNPs for AFB (panel a) and NEB (panel b) in single genomic control, meta-analysis. The grey shaded areas in the Q-Q plots represent the 95% confidence bands around the *P*-values under the null hypothesis.

Figure 3. Genetic overlap between AFB and NEB and other related traits. Results from Linkage-Disequilibrium (LD) Score regressions: estimates of genetic correlation with developmental, reproductive, behavioral, neuropsychiatric and anthropometric phenotypes for which GWAS summary statistics were available in the public domain. The length of the bars indicates the estimates of genetic correlation. Grey error bars indicate 95% confidence intervals. The mark "*" indicates that the estimate of genetic correlation is statistically significant after controlling for multiple testing ($P<0.05/27=1.85x10^{-3}$).

Table 1. GWAS meta-analysis results for independent loci that are genome-wide significantly ($P<5.0x10^{-8}$) associated with AFB or NEB in either the combined or sex-specific meta-analysis.

SNP	Chr	Position (bp)	Nearest Genes	Annotation	Effect Allele / Other Allele	EAF	Beta	*P* value	N (pooled)	Beta (men)	*P* value (men)	Beta (women)	*P* value (women)
Age at first birth (AFB)													
rs10908557	1	153927052	*CRTC2*	N, R, ctQ, ctM	C/G	0.695	0.091	**5.59E-10**	249,025	0.185	2.98E-07	0.076	5.38E-06
rs1160544	2	100832218	*LINC01104*	R, cQ, cM	A/C	0.395	-0.082	**2.90E-09**	250,330	-0.042	2.12E-01	-0.092	**5.00E-09**
rs2777888	3	49898000	*CAMKV*	N, R, ctQ, ctM	A/G	0.507	0.106	**4.58E-15**	250,941	0.155	2.40E-06	0.095	**6.07E-10**
rs6885307	5	45094503	*MRPS30, HCN1*	R, ctQ, cM	A/C	0.799	-0.107	**2.32E-10**	248,999	-0.131	2.07E-03	-0.104	**3.90E-08**
rs10056247	5	133898136	*JADE2*	cQ, cM	T/C	0.289	0.082	**4.37E-08**	249,429	0.050	1.68E-01	0.089	1.28E-07
rs2347867	6	152229850	*ESR1*	cM	A/G	0.649	0.091	**1.38E-10**	248,039	0.098	4.69E-03	0.097	**1.80E-09**
rs10953766	7	114313218	*FOXP2*	cM	A/G	0.429	0.087	**1.82E-10**	248,039	0.106	1.31E-03	0.089	**8.41E-09**
rs2721195	8	145677011	*CYHR1*	R, cQ, ctM	T/C	0.469	-0.073	6.25E-07	250,493	-0.014	6.85E-01	-0.099	**6.13E-09**
rs293566	20	31097877	*NOL4L*	cQ, cM	T/C	0.650	0.081	**1.41E-08**	245,995	0.110	1.47E-03	0.079	1.31E-06
rs242997	22	34503059	*LARGE1, ISX*		A/G	0.613	-0.084	**3.38E-09**	238,002	-0.139	8.51E-05	-0.076	1.82E-06
Number of children ever born (NEB)													
rs10908474	1	153753725	*SLC27A3, GATAD2B*		A/C	0.384	0.020	**2.08E-08**	342,340	0.021	8.10E-04	0.020	7.89E-06
rs13161115	5	107050002	*EFNA5, FBXL17*	cM	C/G	0.234	-0.041	1.34E-02	341,737	-0.041	**1.37E-08**	0.005	3.29E-01
rs2415984	14	46873776	*LINC00871*	cM	A/G	0.470	-0.020	**2.34E-08**	315,167	-0.029	2.41E-06	-0.016	3.71E-04

Note: The rows in bold are the independent signals reaching $P<5\times10^{-8}$ in the meta-analysis. Annotation shows for each of the 12 independent lead SNPs (i.e., excluding rs10908474 on Chr 1) whether it is (i) in strong LD ($r^2>0.8$) with a non-synonymous variant (N) or one or more variants prioritized by RegulomeDB (R) with evidence of having functional consequences (defined as a score <4); (ii) associated with an eQTL in *cis* and/or *trans* (ctQ); (iii) associated with an meQTL in *cis* and/or *trans* (ctM). "EAF" refers to effect allele frequency of the pooled meta-analysis. "Beta" refers to the effect size in the AFB and NEB analyses. All *P* values are from the fixed effects, sample-size–weighted meta-analysis.

Table 2. Function and potential relevance for genes in GWAS-identified loci that are most likely causal based on all available evidence.

Lead SNP	*Gene*	Chr	Evidence	Gene function and potential role in reproduction and (in)fertility	Reference
rs10908557	*CRTC2*	1	G, V, ctQ, ctM, Q lymph. (R)	Functions as a Ca^{2+} and cAMP-sensitive coincidence sensor; Promotes CREB target genes expression; Is a signal mediator in FSH and TGFβ1-steroidogenesis in ovarian granulosa cells.	60
rs10908557	*CREB3L4*	1	N, V, cQ, cM	Plays a role in protein maturation; Involved in spermatid differentiation and male germ cell development; Expressed in prostate, oocytes, fallopian tubes, mammary glands.	46,47
rs10908557	*GATAD2B*	1	V, Q monoc. (R)	Transcriptional repressor and a component of nucleosome remodelling complex Mi2/NuRD. Increased expression in endometriosis; a common gynaecological disorder that causes pelvic pain and infertility.	61, 62
rs10908557	*SLC39A1*	1	V, cQ, cM	Zinc uptake transporter; Major zinc regulator in prostate cells; Involved in the regulation of zinc homeostasis by cumulus cells in the oocyte**.**	63, 64
rs10908557	*DENND4B*	1	cM	A paralogue of *DENN1A*, which has been implicated in polycystic ovary syndrome; Expressed at the protein level in the cervix.	65, 66
rs1160544	*AFF3*	2	cQ, cM	A lymphoid nuclear transcriptional activator gene and implicated in tumor genesis; Same family as *AFF3*, *AFF4* (*FMR2* family member 4); Transcriptional regulator in testicular somatic cells; Essential for male germ cell differentiation and survival in mice.	67, 68
rs1160544	*LINC01104*	2	G, V	Unknown.	
rs2777888	*HYAL3*	3	cM, Q monoc. (R)	Hyaluronidases including HYAL3 are involved in degradation of hyaluronan, a major glycosaminoglycan of the extracellular matrix; Acquired during sperm maturation in the epididymis and involved in sperm function and the acrosome reaction; Required for *in vitro* cumulus penetration in mice, although, its absence is not associated with infertility (perhaps compensated for by other Hyaluronidases).	69
rs2777888	*RBM6*	3	V, cQ, cM, DEPICT, Q monoc. (R)	Involved in RNA splicing.	70
rs2777888	*RNF123*	3	V, cQ, cM, Q liver (R)	Plays a role in cellular transitioning from the quiescence to proliferative state by its E3- ubiquitin ligase activity towards cyclin-dependent kinase inhibitor 1B, which controls the cell cycle	70–72

				progression at G1 phase.	
rs2777888	*RBM5*	3	V, cQ	Involved in cell cycle regulation; Is a regulator of precursor messenger RNA splicing; Involved in spermatogenesis and fertility in mice.	73
rs2777888	*MON1A*	3	V, cM, DEPICT	Involved in the movement and trafficking of proteins (e.g. ferroportin) through the secretory apparatus.	74
rs2777888	*U73166.2*	3	DEPICT	Unknown.	
rs2777888	*MST1R*	3	N, V, cM, MetaRanker, ToppGene and Endeavour	A cell-surface receptor for MSP with tyrosine kinase activity, expressed on the ciliated epithelia of the mucociliary transport apparatus of the lung: Involved in host defence, expressed in sperm. May act as a regulatory system of ciliary motility – together with MSP – which sweeps eggs along the oviduct; Expressed in mucous membrane, mammary glands.	75
rs10056247	*JADE2*	5	G, V, cM,	Involved in histone acetylation.	
rs13161115	*EFNA5*	5	cM	Involved in development and differentiation of the nervous system and folliculogenesis regulation; Required for normal fertility in female mice; Expressed in embryonic stem cells, embryoid bodies.	76
rs6885307	*HCN1*	5	G, cM	Hyperpolarization-activated cation channel that contributes to the native pacemaker current in e.g. neurons; HCN1 channels are present in Kisspeptin (Kiss1) neurons in the rostral periventricular area of the third ventricle (RP3V), which provide an excitatory drive to gonadotropin-releasing hormone (GnRH) expressing neurons that control fertility.	77
rs2347867	*ESR1*	6	G, cM, binds at rs4851269 on Chr2 (R)	Transcription factor involved in estrogen-responsive gene expression. Essential for sexual development and reproductive function in women; Genetic variants in *ESR1* may influence susceptibility to endometriosis or female fertility in endometriosis patients; Involved in male fertility by transferring estrogen effect; Expressed in myometrium, endometrium, oocytes, uterus, fallopian tubes.	53,78–81
rs10953766	*FOXP2*	7	G, cM, binds at rs6997 on Chr 3 (R)	Transcription factor expressed in fetal and adult brain that is involved in speech and language development; Involved in regulation of neuronal development in the embryonic forebrain. Expressed in mucous membrane, myometrium.	82
rs2721195	*CYHR1*	8	cQ, cM	A histidine-cysteine rich protein involved in spermatogenesis.	55
rs2721195	*GPT*	8	V, cQ, cM, Q monoc. (R)	Involved in intermediary metabolism of glucose and amino acids; May play a role in spermatogenesis via testicular glucose metabolism, which is pivotal for the normal occurrence of spermatogenesis; Levels in the normal range are positively associated with metabolic and endocrine abnormalities in women of reproductive age and negatively with FSH levels, independently of obesity.	83,84
rs2721195	*RECQL4*	8	V, cQ, cM	Processing of aberrant DNA structures that arise during DNA replication and repair.; Predominantly expressed in testis.	85

rs2721195	*PPP1R16A*	8	V, cQ, cM, Q monoc. (R)	Regulator of protein phosphatase PP1β;Present in the sperm tail where it interacts with proteins that are important in sperm structure and motility;Expressed in mammary glands, fallopian tubes.	86
rs293566	*NOL4L*	20	cQ, cM	A component of cytoplasm and nucleoplasm;Expressed in Umbilical Veins.	

Evidence categories include: nearest gene (G), non-synonymous variant (N), gene-based GWAS performed in VEGAS (V), eQTL in *cis* and/or *trans* (ctQ), meQTL in *cis* and/or *trans* (ctM), eQTL (Q) in lymphoblasts (lymph), monocytes (monoc) or liver based on RegulomeDB (R), gene prioritization using either DEPICT or MetaRanker, ToppGene and Endeavour, protein binding at SNP based on RegulomeDB (R).

Chr= Human chromosome on which the gene is located.

FSH= Follicle-stimulating hormone; **CREB**=cAMP response element-binding protein; **TGFβ1**= Transforming growth factor β1; **MSP** = Macrophage stimulating protein

SNIPPER was used for the literature search, using the search terms "fertility", "sperm", "ovum" and "reproduction".

Gene Network was used for finding the tissue/organ with high expression of a given gene (AUC >0.8).

ONLINE METHODS

GWAS of reproductive behavior study design in brief

Genome-wide association analyses of age at first birth (AFB) and number of children ever born (NEB) were performed at the cohort level according to a pre-specified analysis plan (see Supplementary Note). Cohorts uploaded results imputed using the HapMap 2 CEU (r22.b36) or 1000G reference sample. Cohorts were asked to only include participants of European ancestry, with no missing values on all relevant covariates (sex, birth year, and cohort specific covariates), who were successfully genotyped genome-wide, and passed cohort-specific quality controls. We followed the QC protocol of the GIANT consortium's recent study of human height[87] and employed QCGWAS[88] and EasyQC[89] software, which allowed us to harmonize the files and identify possible sources of errors in association results.

Cohort association results (after applying the QC filters) were combined using sample-size weighted meta-analysis with genomic control (GC) correction within each study, implemented in METAL.[90] SNPs were considered genome-wide significant at *P*-values smaller than 5×10^{-08} (α of 5%, Bonferroni-corrected for a million tests). The meta-analyses were carried out by two independent analysts. Detailed results of each genome-wide significant locus are shown in in Supplementary Figures 4-29.

The total sample size of the meta-analysis is *N*=251,151 for AFB pooled and *N*=343,072 for NEB pooled. The PLINK clumping function[91] was used to identify the most significant SNPs in associated regions (termed "lead SNPs"). Detailed cohort descriptions, information about cohort-level genotyping and imputation procedures, cohort-level measures, and quality control filters are shown in Supplementary Tables 26, 27 and discussed in the Supplementary Note.

Dominant genetic variation in fertility

We applied a method recently developed by Zhu and colleagues[92] to estimate dominant genetic effects based on the genetic relatedness of unrelated individuals. Our results based on the combined samples of TwinsUK and Lifelines show no evidence for dominant genetic effects for either NEB ($1.0\text{x}10^{-07}$, SE=0.07, *P*=0.45) nor AFB (0.02, SE=0.08, *P*=0.43. Results are shown in Supplementary Table 28 and discussed in the Supplementary Note.

Bivariate and conditional analysis

As joint analysis of correlated traits may boost power for mapping functional loci, we applied a recently developed multi-trait analysis method[93] to test the association between each variant and the two correlated traits AFB and NEB simultaneously using multivariate analysis of variance (MANOVA) (see Supplementary Note and Supplementary Table 29). The analysis was performed based on the genome-wide meta-analysis summary statistics of each single trait. Although it did not reveal additional genome-wide significant loci (λ=0.995), it accounted for the correlation between the two phenotypes, thus improving the strength of two signals on chromosomes 1 and 5, indicating possible pleiotropic architecture between AFB and NEB (Supplementary Figure 30). The analysis also provided a conditional association

test of the genetic effect of each variant on AFB including NEB as a covariate, and on NEB including AFB as a covariate (Supplementary Figure 31)

Population stratification

We used two methods to assess whether our GWAS results exhibited signs of population stratification (see Supplementary Note). First, we used the LD Score intercept method described in Bulik-Sullivan *et al*.[94] to test whether inflation in chi-square statistics was due to confounding biases such as cryptic relatedness and population stratification. In all six cases, the intercept estimates were not significantly different from 1, suggesting no appreciable inflation of the test statistics attributable to population stratification. Second, we conducted a series of individual and within-family (WF) regressions using polygenic scores (PGS) as predictors[95–97] on a dataset of DZ twins (STR and TwinsUK). The regression analyses showed that WF regression coefficients for both AFB and NEB were statistically different from zero when the *P*-value threshold was sufficiently high (Supplementary Tables 30, 31 and Supplementary Figures 32, 33).

Sex-specific effects

In addition to the pooled GWAS results presented in the main text, we also ran sex-specific GWAS meta-analyses for AFB and NEB (see Supplementary Note). The sample size for sex-specific analysis was: AFB women, *N*=189,656; AFB men, *N*=48,408; NEB women *N*=225,230; NEB men *N*=103,909. Our results indicated 6 genome-wide significant ($P<5x10^{-08}$) independent SNPs for AFB women and 1 genome-wide significant independent SNP for NEB men (Supplementary Table 32 and Supplementary Figures 34, 35). We also used LD score bivariate regression and GREML bivariate analysis to estimate the genetic correlation among men and women based on the sex-specific summary statistics of AFB and NEB meta-analysis results. Our estimates based on LD bivariate regression indicated a genetic correlation of r_g=0.86 (SE=0.052) among the sexes for AFB and r_g=0.97 (SE=0.095) for NEB. Results are shown in Supplementary Tables 33, 34 and discussed in the Supplementary Note.

Polygenic score prediction

We performed out-of-sample prediction and calculated polygenic scores for AFB and NEB, based on GWA meta-analysis results and used regression models to predict the same phenotypes in four independent cohorts: HRS, Lifelines, STR and TwinsUK (see Supplementary Note and Supplementary Figure 2). We ran ordinary least-squares (OLS) regression models and reported the R^2 as a measure of goodness-of-fit of the model. In addition, we tested how well our polygenic scores for NEB could predict childlessness at the end of the reproductive period (using age 45 for women and 55 for men), Supplementary Table 21. Since age at first birth is observed only in parous women, we adopted an additional statistical model to account for censoring (Cox Proportional hazard model, Supplementary Table 22) and selection (Heckman selection model, Supplementary Table 35). We additionally tested the predictive value of our polygenic scores for AFB for age at menarche (using TwinsUK) and age at menopause (using Lifelines), Supplementary Table 23. Finally,

we examined whether menopause variants are associated with AFB. We calculated a PGS of age at menopause based on the recent GWAS results from Day et al. (2015)[98] and applied them to LifeLines and TwinsUK (Supplementary Table 36).

Genetic correlations

We used information from 27 publicly-available GWAS results to estimate the amount of genetic correlations between AFB and NEB and related traits (Supplementary Table 25 and Figure 3 in the main text) using LD score bivariate regression (see Supplementary Note). Details on these phenotypes are provided in the Supplementary Note. A conservative Bonferroni-corrected *P*-value threshold of $P<1.85\times10^{-03}$ (=0.05/27) was used to define significant associations. We also tested the correlation between NEB and AFB using a bivariate GREML analysis on the Women's General Health Study (WGHS, *N*=40,621).

Lookups and proxy phenotype

Following the results on genetic overlap with other phenotypes we tested – in a quasi-phenotype replication setting – whether the SNPs strongly associated with AFB in women were empirically plausible candidate SNPs for age at menarche and age at menopause (see Supplementary Note). We used a two-stage approach applied in other contexts.[99,100] In the first stage, we conducted a meta-analysis of AFB excluding the cohorts that were part of the meta-analysis of the phenotype we intended to replicate. We merged the SNPs from this meta-analysis with the publically available association results of the most recent GWAS on age at menarche[2] and age at menopause[101] from the Reprogen consortium website.[1] SNPs that were not present in both files were dropped from the analysis. We aligned the alleles and the direction of effects using the EasyStrata software.[102] We then selected the independent SNPs with a *P*-value$<1x10^{-05}$, using the clump procedure in PLINK[91], (1000Kb window and LD threshold of $R^2>0.1$) to identify the most significant SNPs in associated regions included in both files. We defined "prioritized SNP associations" as those that passed the Bonferroni correction for the number of SNPs tested ($0.05/122=4.10x10^{-04}$, both in age at menarche and age at menopause). Our results identified three SNPs after Bonferroni-correction that can be used as good candidates for age at menarche. We did not isolate any clear "candidate SNP" for age at menopause (Supplementary Figure 36).

Gene-based GWAS analysis

We performed gene-based testing with the full GWAS set (~2.5M HapMap-imputed SNPs) of both phenotypes using VEGAS (see Supplementary Note and Supplementary Tables 3,4).[23,103] This software has the advantage of accounting for LD structure and the possibility to define a range beyond the gene bounds to include intergenic regions in the analysis. We defined a 50kb extra window surrounding the genes and considered every SNP for the gene-based analysis, ran the analyses per chromosome with up to 10^{06} permutations and considered $P<2.5x10^{-06}$ as the threshold for significance (0.05/~20.000 genes).

[1] Data downloaded in November 2015

eQTL and meQTL analysis

For each of the 12 SNPs identified in the GWAS, local (*cis*, exons/methylation sites < 1 MB from the SNP) and genome-wide (*trans*, exons/methylation sites > 5 MB from the SNP) effects were identified by computing Spearman rank correlations between SNPs and local or global exons/methylation sites (see Supplementary Note). Bonferroni multiple testing correction was performed for the 12 SNPs tested ($P<2.5x10^{-06}$ for *cis* meQTL analysis, $P<1x10^{-08}$ for *trans* meQTL analysis, $P<1.2\ x10^{-06}$ for *cis* eQTL analysis, $P<1.3x10^{-08}$ for *trans* eQTL analysis). For each of the significant associations, the exons/methylation sites were selected, the strongest eQTLs were identified for these exons/methylation sites, and LD between the strongest eQTLs and the corresponding SNP identified in the GWAS were computed. LD was computed using BIOS genotypes (the genotypes used for eQTL and meQTL mapping).

Functional variant analysis using RegulomeDB

We used RegulomeDB[27] to identify variants amongst the 322 SNPs that reached $P<5x10^{-08}$ for association with AFB and/or NEB in the meta-analysis of GWAS that likely influenced regulation of gene expression (see Supplementary Note). RegulomeDB integrates results from RoadMap Epigenomics[26] and the ENCODE project.[104] SNPs showing the most evidence of being functional – defined as a RegulomeDB score <4 – were subsequently examined in more detail in terms of effects on gene expression (eQTLs) and their protein-binding capacity (Supplementary Table 6).

Gene prioritization

Potentially causal genes for the associations identified by GWAS were identified using four previously described bioinformatics tools: ToppGene[4], Endeavour[5], MetaRanker[6], and DEPICT[7]. To this end, we first retrieved positional coordinates for all lead SNPs according to GRCh37/hg19 using Ensembl's BioMart. These coordinates were used to extract all genes located within ±40kb of lead SNPs using the UCSC table browser. The identified genes then served as input for ToppGene and Endeavour. Genes with established roles in fertility served as training genes in this procedure, i.e. *BRCA1*, *EGFR*, *ERBB2-4*, *HSD17B1*, *RBM5*, *ESR1*, *ESR2* and *FSHB*. For MetaRanker we provided SNPs that reached $P<5x10^{-04}$ and their chromosomal position as input, together with the previously mentioned set of training genes. Since ToppGene, Endeavour and MetaRanker are biased towards larger and well-described genes, we also performed a gene prioritization procedure using DEPICT.[7] All SNPs that reached $P<5x10^{-04}$ in the meta-analysis served as input, and information on prioritized genes, gene set enrichment, and tissue/cell type enrichment were extracted. Genes were subsequently prioritized that: 1) reached $P<0.05$ in DEPICT; or 2) reached $P<0.05$ in ToppGene, Endeavour and MetaRanker (Supplementary Table 37).

Functional network and enrichment analysis

DEPICT was used to identify gene set, cell type and tissue enrichment analyses, using the GWAS-identified SNPs with $P<5x10^{-04}$ as input (see Supplementary Note). Due to the relatively small number of identified loci, DEPICT was only able to perform these analyses

for AFB and NEB pooled, and AFB women. To construct a functional association network, we combined five prioritized candidate gene sets into a single query gene set which was then used as input for the functional network analysis.[24] We applied the GeneMANIA algorithm together with its large set of accompanying functional association data.[105] We used the Cytoscape software platform,[106] extended by the GeneMANIA plugin (Data Version: 8/12/2014, accessed April 24, 2016).[107] All the genes in the composite network, either from the query or the resulting gene sets, were then used for functional enrichment analysis against Gene Ontology terms (GO terms)[108] to identify the most relevant GO terms using the same plugin.[107]

Gene-environment interactions

Previous research based on twin studies shows differential heritability of fertility behavior across birth cohorts.[109,110] We used the Swedish Twin Register (STR) to examine whether the effect of a polygenic score (PGS) of AFB and NEB varies across birth cohort. We followed the analysis presented in the recent GWAS of education[111] and divide the sample into six groups based on their year of birth. Each group spans five birth years, with the oldest ranging from 1929-1933 and the youngest born between 1954-1958. Supplementary Table 38 reports the estimated coefficient from these regressions. The results indicate a U-shaped trend in AFB and a linear decline in NEB, but do not provide any clear evidence of interaction effects between the PGS's and birth cohort. We additionally tested the interaction effects between educational level and the PGS of AFB and NEB in three different samples (LifeLines, STR and HRS). Supplementary Table 39 reports the estimated coefficient from these regressions. The results indicate that years of education are positively associated with AFB in both LifeLines and STR, and negatively associated with NEB in the HRS. With the exception of NEB in the HRS, we found no evidence of GxE effects with education.

Robustness checks

To estimate the robustness of our results for AFB, we conducted two additional analyses. First, we estimated how the coefficients change if we control for Educational Attainment (EA). Using data from deCODE, we ran an additional association analysis using the 10 loci that were genome-wide significant in the meta-analysis ($P<5x10^{-08}$). The analysis has been restricted to individuals born between 1910 and 1975, who also had data available on completed education. The total sample size is 42,187 (17,996 males and 24,191 females). The analysis is adjusted for sex, year of birth (linear, squared and cubic), interaction between sex and year of birth and the first 10 PCAs. Education is measured by years of education, ranging between 10 and 20 years. Supplementary Table 40 reports the association results before and after adjusting for educational attainment. Our analysis shows that the effect sizes shrink after including educational attainment as a covariate, with an average reduction of around 15%. We also estimated the effect of a polygenic risk score of AFB calculated from meta-analysis data excluding the deCODE cohort. The polygenic score remains highly significant. The effect of 1SD of the AFB score decreases from 0.19 years (69 days) without controlling for education to 0.16 years (59 days) when we control for years of education. Second, we estimated how the coefficients change after controlling for Education Attainment (EA) and

Age at First Sex using the UKBiobank (*N*=50,954). We ran two association models: the first follows the GWAS analysis plan with no additional covariates and the second added years of education and age at first sexual intercourse as covariates. The results are presented in Supplementary Table 41 and Supplementary Figure 37. Our analysis shows that the effect sizes of our top hits are highly concordant (R^2=0.94). The inclusion of EA and AFS as covariates weakens the effect sizes on average by 40% and increases the *P*-value of the estimated coefficients. Overall, we interpret this additional analysis as a robustness test that confirm that the top hits from our meta-analysis are robust to the inclusion of the confounding factors of EA and AFS.

Positive selection

We performed a Haploplotter analysis[112] to examine if lead SNPs and/or functional variants identified using RegulomeDB show evidence of positive selection. Three variants showed standardized integrated haplotype scores <-2 or >2, indicating that these variants represent the top 5% of signals in the population. These SNPs are: 1) rs7628058 on chromosome 3 for AFB, an eQTLs for *RBM6* in monocytes; 2) rs2247510 on chromosome 3 for AFB, an eQTL for *RBM6* and *HYAL3* in monocytes and binding site for a range of transcription factors; 3) rs2415984, the lead SNP in the chromosome 14 locus for NEB. Results are presented in Supplementary Table 42.

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Supplementary Note

"Genome-wide analysis identifies 12 loci influencing human reproductive behavior"

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1. HUMAN REPRODUCTIVE BEHAVIOR MOTIVATION AND PHENOTYPE DEFINITION

1.1 Phenotype Motivation

Human reproductive behavior – measured by age at first birth (AFB) and number of children ever born (NEB) – is a core topic of research across the medical, social and biological sciences.[1] Two central indicators are the tempo of childbearing of age at first birth (AFB) and the quantum or number of children ever born (NEB). NEB is also often referred to in biological research as life-time reproductive success,[2] number of offspring[3] or as 'fitness' in evolutionary studies, which is the function of the number of children of a person in relation to the number of children of peers of the same birth cohort.[4,5] Due to improvements in hygiene and the reduction in prenatal, infant and child mortality in industrialized societies, NEB has emerged as the gold standard to measure lifetime reproductive success indicating biological fitness.[5]

AFB and NEB are complex phenotypes related not only to biological fecundity, but also behavioral in that they are driven by the reproductive choice of individuals and their partners, and shaped by the social, cultural, economic and historical environment. Genetic factors influence the first two factors of biological fecundity and choice, with the social and historical environment filtering the types of behavior that are possible (e.g., via contraceptive legislation, social norms).

Although interrelated, AFB and NEB, but also childlessness, are distinct phenotypes. Late AFB, low NEB or remaining childless is not only due to 'involuntary' infertility or factors outside of the individual's control (e.g., inability to find a partner), but also 'voluntary' choices to remain 'childfree'.[6] In the past four decades there has been a rapid postponement by around 4-5 years in the AFB to advanced ages in many industrialized societies[7] and a growth in childlessness, with around 20% of women born from 1965-69 in Southern and Western European countries having no children.[8] The biological ability to conceive a child starts to steeply decline for some women as of age 25, with almost 50% of women sterile by the age of 40.[9] Birth postponement and a lower number of children has been largely

attributed to social, economic and cultural environmental factors (i.e., individual and partner characteristics, socioeconomic status).[7,10] Not surprisingly, this delay has led to an unprecedented growth in infertility (i.e., involuntary childlessness), which impacts between 10-15% of couples in Western countries, with men and women affected equally.[8] An estimated 48 million couples worldwide are infertile,[11] with a large part of subfertility, particularly in men, remaining unexplained.[12] Although therapeutic options for infertility in the form of Assisted Reproductive Technology (ART) are available, they are highly ineffective at later ages and older mothers have considerably more problems during gestation and delivery, also associated with low birth weight and preterm delivery.[13–15] Recent studies have also linked advanced maternal age to a higher risk of schizophrenia in offspring.[16]

Childless individuals (and those with a low NEB) are a heterogeneous group consisting of the involuntary childless (e.g., infertility, sterility) and voluntarily childless or 'childfree' (e.g., out of choice). Although primarily related to biological fecundity, involuntary childlessness may also be due to circumstantial socio-environmental reasons outside of the individual's control, including a lack of ability to find a stable partner,[17] divorce and lack of housing, employment or material resources to start a family.[18] Those who are voluntarily childless are generally considered to have made an active choice or to be endowed with an underlying preference[19] or personality traits that pull individuals towards or away from parenthood.[20] It is difficult to disentangle the voluntary from the involuntary, however, since fertility intentions can be adjusted in relation to circumstances[21] and these modifications are age-related.[22]

A better understanding of the genetic architecture of human reproductive behavior and its relation to the environment would enable the discovery of predictors of infertility, which would in turn greatly improve family planning but also reduce costly and invasive ART treatments. Examination of AFB and NEB may also produce a better understanding of the biology of human reproduction, which in turn may give insight into fundamental biological mechanisms and could have ramifications for the study of many health outcomes, especially the etiology of diseases related to the reproductive tract. Furthermore, it is important to understand whether and which proportion of these traits are driven by genetic, behavioral and environmental factors. Relatively little is known about the relationship between indicators of

women's reproductive lifespan (menarche, menopause) and reproductive success. A smaller and recent study has produced some evidence of the link between age at first sexual intercourse (AFS) with AFB and NEB, with a focus on puberty and development.[23]

By systematically investigating the relationship with genetic variants for a multitude of phenotypes related to human reproduction we can establish to what extent diseases related to the reproductive tract play a role in human reproduction and vice versa, and begin to chart the complex biological and related mechanisms that drive human reproduction. It is therefore crucial to examine not only genetic determinants of more biologically proximate phenotypes (e.g. age at menarche, endometriosis, PCOS) but also human reproductive behavior and success. AFB and NEB represent more accurate and concrete measures of observed reproductive success in comparison with proxies which capture the reproductive life span (e.g., age at menarche, menopause) or infertility measures (e.g., endometriosis, PCOS).

To our knowledge, the current study is the largest meta-GWAS effort on human reproductive behavior, which we launched in early 2012. As mentioned previously, a recently published smaller and related study of cohorts also involved in our study focused on age at first sex (AFS), also linking it to AFB and NEB (among other traits).[23] The AFS study examined how individual variation in pubertal timing and personality characteristics related to high risk-taking and low neuroticism related to reproductive activity and success with AFS measures, measures integrated into our examination of genetic correlations (see Supplementary Note, section 7).

Several studies have shown promising results for fertility-related outcomes related to both infertility and the reproductive life span. Previous research has uncovered a genetic component to reproduction with over 70 genome-wide association studies (GWAS) published for 32 traits and diseases associated with reproduction (for a review see ref. [24]). This includes identification of genes such as those related to age at menarche[25,26,27], menopause[28–32], endometriosis[33–36] and polycystic ovary syndrome[37]. This study is the first step towards understanding the pathways between genes and the complex relationship between reproduction and other phenotypes and the environment.

1.2 Evolutionary causes of genetic variance in fertility

Given the diminishing child mortality rate in contemporary societies, evolutionary biologists have used NEB as a proxy for fitness.[2,5,38] Additive genetic variance in fitness implies natural selection within populations: alleles that lead to higher reproductive success will have a higher frequency in future generations.[39] Researchers have until now arguably given less attention to NEB than it deserves,[1] perhaps due to a frequent erroneous interpretation of Fisher's[40] Fundamental Theorem of Natural Selection. The theorem states that the increase in population mean fitness ascribable to changing allele frequencies is equal to the additive genetic variance in fitness. It has often been misinterpreted, however, to mean that the additive genetic variance in fitness itself should always be close to zero. A close reading of the text shows that Fisher actually argued that fitness is moderately heritable in human populations. The misinterpretation of Fisher's theorem is likely repeated so often due to its intuitive appeal. Naively, it may seem that genes that reduce fitness should have been less frequently passed on, leading to the elimination of genetic variability in traits such as fertility.[40,41] Nevertheless, we find that fitness traits such as NEB and AFB have significant narrow-sense heritabilities – yet these traits are still not as heritable as morphological traits such as height.[38,42–44] Several reasons have been put forward to explain the persistent genetic variance in fertility. One argument is that new mutations suffice to restore any genetic variance lost to selection.[45] For the current study design, additional aspects to consider are sexual antagonistic genetic effects, non-additive genetic effects, environment and gene-environment interaction. As discussed in more detail in the Supplementary Note (Section 5), the current GWAS was conducted separately for both sexes, with a detailed examination explored within that section.

1.3 Additive genetic variation in fertility

Several twin and family studies provide evidence for a genetic component underlying both the tempo (AFB) and quantum (NEB) of human fertility.[1,3] Heritability – the proportion of the variance in a trait explained by genetic variance – is typically assessed by a comparison of the phenotypic correlations of family members of different genetic relatedness (for example genetically identical or monozygotic and genetically fraternal dizygotic twins). The genetic component is the extent to which genetically identical twins are more similar in their fertility behavior. As summarized in Fig. S1.1, heritability estimates for AFB (for women)

are around 0.25 and for NEB ranging from 0.15 to 0.45.[1] A recent meta-analysis of all twin studies conducted until 2012[44] shows average heritability of 0.45 (SE = 0.027, N = 50,265) among 64 reproductive disease traits of women and of 0.36 (SE= 0.054, N = 9,376) among 25 reproductive disease traits of men. These mainly pertain to diseases of the genitourinary system, endocrine, nutritional and metabolic diseases, and only few directly pertain to pregnancy, childbirth and the puerperium.

With the advent of molecular genetic data and complementary analytical tools,[46] it has become feasible to go beyond twin models to produce heritability estimates to apply the same logic to unrelated individuals based on the genetic relatedness matrix across all individuals estimated from common SNPs from the whole genome.[47,48] A recent study combined data from the Lifelines Cohort Study and the TwinsUK to estimate this so called SNP-based heritability as the lower bound of narrow sense heritability.[38] Results show that 10% of the variance in NEB and 15% of the variance in AFB are associated with common additive genetic variance. Given that SNP-based heritability is estimated from the same genomic information as utilized in GWAS studies, these results suggest that we should be able to find genetic variants associated with human fertility when conducting GWAS meta-analyses of sufficient sample size.

1.4 Dominant genetic variation in fertility

GWAS typically assume additive genetic effects. Dominant models, however, are in principle also applicable.[49] Dominant genetic effects and overdominance (heterozygote advantage) are mechanisms which potentially maintain non-additive genetic variation in fertility and other fitness related outcomes.[40] Dominant genetic effects result if the conditional phenotypic mean of the heterozygote is not exactly intermediate between those of the homozygotes. Overdominance refers to the special case of the heterozygote possessing a fitness advantage over both homozygotes. At the equilibrium under selection, overdominance leads to an absence of additive genetic variance. Any deviation from strict additivity within a locus, however, should lead to dominance variance that is in principle detectable.[45]

Previous studies approaching the genetic architecture of human fertility almost exclusively relied on twin designs.[1] Dominant genetic effects are detectable in twin studies if the correlation in a trait among identical twins exceeds twice the correlation of fraternal twins. Correlations amongst family members, however, can by inflated by shared environmental factors and therefore hide dominant effects – a potential reason why previous twin studies did not find effects.[49]

Recently, Zhu and colleagues[49] developed a method to estimate dominant genetic effects based on the genetic relatedness of unrelated individuals. This is a complementary approach to the established GREML analysis, which estimates additive genetic effects on traits. In the article of Zhu and colleagues, they quantify dominant relative to additive variance components for 79 quantitative traits and find little evidence for dominant effects. We applied the GREML model to investigate additive genetic effects on NEB and AFB in combined cohorts of women from the TwinsUK and the Lifelines study in the Netherlands.[38] On a slightly larger sample – with a relaxed relatedness cut-off of 0.05[50] and the exclusion of women younger than 45 for AFB – we replicated previous findings with a SNP-heritability of 0.09 for NEB and 0.17 for AFB. However, we find no evidence for dominant genetic effects δ^2_{SNP} for either NEB (0.1×10^{-06}, SE 0.07, P=0.45) nor AFB (0.02, SE=0.08, P=0.43, see Supplementary Table 28 for results). We can therefore conclude that due to this lack of evidence of dominant genetic effects, it is not problematic that we have excluded dominant models in our GWAS.

1.5 Environmental variations in fertility

Social scientists, such as demographers and sociologists, have attributed later ages of first birth, lower NEB and growing levels of childlessness in many industrialized societies almost exclusively to socio-environmental factors.[7,10] The underlying socio-environmental forces shaping fertility can be divided into four main factors. First, the introduction of efficient and reliable contraceptives in the early 1960s revolutionized human reproductive behavior, namely the ability to control the timing and number of children.[7] The diffusion of the pill in the late 1960s in the United States resulted in an almost immediate postponement in the age of first marriage for college-educated women.[51] Contraception allowed women and couples

to avoid pregnancy and delay entry into parenthood. Contraceptives were generally widely introduced across Western and Northern Europe, Australia and North America in the late 1960s, which is where the majority of cohorts are situated in the current study.

Second, there is a well-documented association between female education and later AFB.[52] Early research demonstrated a strong inverse relationship between education and fertility, with women's increased participation in higher college and University degrees resulting in a significant shift to later AFB.[53–55] A central argument driving childbearing delay was the difficulty to balance student and mother (parent) roles, but also women's opportunity costs in terms of wages and career progression that they forego when having children early.[56–58] A third factor, which is interdependent with educational level, is women's labor force participation and attachment. Research has demonstrated an incompatibility of early AFB and high NEB with paid labor force participation,[59] largely due to work-family conflict[7] and the high motherhood 'wage penalty'. In fact, the postponement of AFB results in substantial increases in earnings, particularly for higher-educated women.[60,61] It is estimated that there is a 7% motherhood wage penalty per child, with a year delay of entry into motherhood increasing career earnings by 9%.[61]

A fourth factor is the Second Demographic Transition, which encompasses cultural and ideational changes surrounding the preferences for and role of children, which is coupled with a shift to more individualistic desires for personal development.[62,63] Since infant mortality rates have fallen sharply in modern societies, extra births are not required for insurance against death and children no longer provide the economic support and labor to support parents that they once did, which dramatically changes preferences and the need to have children.[64,65] Multiple national institutional factors have also been shown as related to the delay of AFB and the decrease in NEB. This includes changes in the educational systems, labor market regulations, gender equity,[66] but also economic uncertainty,[67] the housing market,[68] influence by friendship networks,[69] family networks and social capital,[70] and changes in partnering and mating practices.[71] The empirical relationship of these factors – namely birth cohort and educational level – with genetic risk scores of AFB and NEB is elaborated upon in section 10.

1.6 Phenotype definition

The current study measures human reproductive choice by the two phenotypes of: age at first birth (AFB) and number of children ever born (NEB). AFB is the self-reported age when subjects had their first child. In most cohorts this was asked directly (e.g. *"How old were you when you had your first child?"*). Alternatively, it could also be calculated based on several survey questions (such as the date of birth of the subject and date of birth of the first child). Supplementary Table 2 describes in detail the exact question asked for each cohort and if applicable, whether and how it varies in the way it was asked to men and women. Often these questions were part of a medical questionnaire about women's reproductive health. In a large number of cohorts, this means that only women were asked this question. For this reason, the sample size for AFB for women is considerably larger than for men. Note that only people who have had at least one child (parous) are eligible to be included for the analysis of this phenotype.

Number of children ever born (NEB) was the self-reported number of children. This phenotype was either asked directly (e.g. "*How many children do you have?"* or "*How many natural (biological) children have you ever had, that is, all children who were born alive?*", or "*How many children have you had - not counting any step, adopted, or foster children, or any who were stillborn?*") or it was calculated based on several survey questions (such as pregnancy histories and outcomes, number of deliveries). In most cases it was possible to distinguish between biological (live born or stillborn) and adopted or step-children. When it was possible to distinguish between cases, we used the number of live born biological children. We included cases for NEB if they finished their reproductive career (aged at least 45 for women and 55 for men at time of study) and were thus unlikely to have future biological children.

1.7 Instructions for contributing cohorts

The instructions given to cohorts who agreed to participate in our study is described in detail in the original Analysis Plan that was posted on the Open Science Framework preregistration site, described in detail in Supplementary Note Section 2.1 and uploaded December 9, 2013 at: https://osf.io/53tea/. For ease of analysis, we advised that AFB should be treated as a

continuous measure. When possible, we asked analysts to use the more direct question: How old were you when you had your first child? Another variant of this question is: What is the date of birth of your first child? In the case of the latter, we advised them to create the AFB variable by subtracting the date of birth of the first child from the date of birth of the subject.

Analysts then normalized the raw measure of the age at first birth for sex/ birth cohort specific means and standard deviations. In other words, we asked them to compute a mean and standard deviation separately for men and women by birth cohort category (generally ten-year intervals) and then subtract the mean value for that group from the respondent's value. They should then divide the result by the standard deviation. This was used as the final AFB variable measured in sex/cohort specific Z-score and is our regressand.

Analysts were asked to include birth year of the respondent (represented by birth year – 1900), its square and cubic to control for non-linear birth cohort effects. Combined analyses that included both men and women also needed to include interactions of birth year and its polynomials with sex. Some cohorts only used birth year and not its polynomials because of multi-collinearity issues/convergence of the GWA analysis.

2. PRIMARY GWAS OF HUMAN REPRODUCTIVE BEHAVIOR

2.1 Overview of human reproductive behavior analyses

The genome-wide association study (GWAS) of human reproductive behavior is based on the summary statistics that were uploaded to a central server by cohort-level analysts. As outlined in more detail in Section 1 of the Supplementary Note, our analysis includes the two phenotypes of age at first birth (AFB) and number of children ever born (NEB), with analysts producing results for women, men and combined analyses of both sexes, also including birth cohort as a covariate. The summary statistics were then subsequently quality-controlled and meta-analyzed by two separate independent centers at the University of Oxford and Erasmus University Rotterdam.

We follow the QC protocol of the GIANT consortium's recent study of human height[72] and employed the software packages QCGWAS[73] and EasyQC[74], which allowed us to harmonize the files and identify possible sources of errors in association results. This procedure entailed that diagnostic graphs and statistics were generated for each set of GWAS results (i.e., for each file). In the case where apparent errors could not be amended by stringent QC, cohorts were excluded from the meta-analysis (see the bottom of Supplementary Table 1 for a list of excluded cohorts).

The lead PI of each cohort confirmed that the results on these analyses were approved by the local Research Ethics Committee and/or the relevant Institutional Review Board. All participants fell under the written informed consent protocol of each participating study. The entire project was also approved by the local Research Ethics Committee of the PI.

We first circulated three documents to interested cohorts at the end of April 2012, which included: (a) Rationale for a GWAS of Fertility Behavior, (b) GWAS Fertility Behavior Analysis Plan; and, (c) Collaboration Agreement for Fertility GWAS Meta-analyses. This was after a meeting and approval from the REPROGEN working group of the CHARGE consortium on Dec. 9, 2011 that we were not competing with or unduly replicating existing efforts. Preliminary results were presented at various CHARGE meetings between the years

of 2012-2015. This study was initially set up as a two-stage GWAS with a large discovery and smaller replication phase. Due to an increasing influx of new data, we opened the participation to cohorts that had genome-wide data, but also to cohorts that had Metabochip data. We also included a list of 15 independent SNPs with $P<10^{-06}$ for cohorts that did not have genome-wide data available but could perform *de-novo* replication on a limited number of SNPs. Agreements at a later stage included data from RPGEH (Kaiser Permanente Research Program on Genes, Environment, and Health, REPEGH/GERA), *N*(AFB women)=31,898, *N*(NEB women)=39,576), deCODE (*N*(AFB pooled)=60,602, *N*(NEB pooled)=65,228), and UK Biobank (*N*(AFB women)=40,082, *N*(NEB pooled)=88,094). Given the resulting well-powered total sample size of *N*≈250k for *AFB* and *N*≈340k for *NEB,* we chose to merge the discovery and replication cohorts into a single large discovery phase, as in other recent well-powered GWAS efforts.[72,75,76] We also opted to include only cohorts with genome-wide data in the meta-analysis, leaving the remaining cohorts that performed *de-novo* replication for follow-up analysis.

2.2 Participating Cohorts

A total of 62 cohorts contributed to this study. Cohorts with acceptable measures of AFB and/or NEB were eligible to participate. Some measured one or both of the phenotypes, and there was also variation by whether the question was asked to women and/or also men. Supplementary Table 1 provides an overview of the study-specific details of all analyses conducted for the traits of interest. Cohorts of unrelated individuals uploaded separate results for men and women. In addition to sex-specific association results, family-based cohorts uploaded pooled results. As described in the Supplementary Note (Section 1), particularly AFB is less frequently asked of men. The total number of association-result files per trait is as follows. We have 28 files for AFB men, 57 for AFB women, 72 for AFB pooled, 50 for NEB men, 67 for NEB women, and 102 for NEB pooled.

As Supplementary Table 1 shows, most cohorts were included in the meta-analysis (i.e., 62 cohorts are included, constituting 26 files for AFB men, 50 for AFB women, 64 for AFB pooled, 47 for NEB men, 60 for NEB women, and 91 for NEB pooled) and some only in the follow-up analyses (9 cohorts, constituting 2 files for AFB men, 5 for AFB women, 6 for

AFB pooled, 3 for NEB men, 5 for NEB women, and 9 for NEB pooled). We had to exclude the association results of two cohorts – ABCFS (AFB women, *N*=410, NEB women, N=410) and Longenity (AFB women, *N*=285; NEB women, N=352) – from the meta- and follow-up analyses due to unresolvable issues with the cohort's association results that came up in the quality control procedures. For more details regarding the reasons for exclusion, see SI Section 2.6.

2.3 Genotyping and Imputation

Supplementary Table 1 gives an overview of the study-specific details on pre-imputation quality control filters applied to the genotype data, subject-level exclusion criteria, imputation software used, and the reference sample for imputation. Due to the fact that we started our study in 2012 before 1000G imputation, our analysis plan recommended using resulted imputed using the HapMap 2 CEU (r22.b36) reference sample.[77]

2.4 Association analyses

Cohorts were asked to only include participants of European ancestry, with no missing values on all relevant covariates (sex, birth year, and cohort specific covariates), who were successfully genotyped genome-wide (e.g., genotyping rate greater than 95%), and who passed cohort-specific quality controls (e.g., no genetic outliers).

Cohorts used the fully imputed set of HapMap Phase 2 autosomal SNPs, and estimated an additive linear model, including top principal components to control for population stratification and cohort specific covariates if appropriate. They were specifically instructed to control for population stratification for ancestry principal components with reference to Price et al. (2006).[78] In addition, cohorts were requested to include the birth year of the respondent (represented by birth year – 1900), its square and cubic to control for non-linear birth cohort effects. Analyses pooling data across sexes also needed to include interactions of birth year and its polynomials with sex. 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 as 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.

2.5 Quality Control

In this section, we summarize the main steps and diagnostic tests of the Quality Control (QC) procedure. The quality control was conducted in two separate independent analysis centers (Oxford/Groningen and Rotterdam). Once data were submitted, each study was independently subjected to quality control in the two analyses centers according to standard protocols. We followed the QC protocol of the GIANT consortium's recent study of human height[72] and the SSGAC's study of educational attainment.[76,79]

Since this study began, QC procedures have become more stringent. Recently, a comprehensive set of guidelines for GWAS QC was released.[7] For the cohorts initially included in the study a first round of QC was performed using the R package QCGWAS[73]. We updated the QC protocol based on the GIANT consortium's and SSGAC's protocols. The updated QC protocol was applied to all cohorts using the R package EasyQC.[74] Findings of the first round of QC were used as a starting point for the updated QC.

In the QC procedure, diagnostic graphs and statistics were generated for each set of GWAS results (i.e., for each result file uploaded by the cohort analysts). Most errors (e.g., coded allele reported as other allele and vice versa) could be easily addressed. When apparent errors could not be amended by combining stringent QC with file-specific inspections and corrections, cohorts were excluded from the meta-analysis. For details on cohort inclusion and exclusion, see Supplementary Table 1.

Filters

We harmonized base pair positions of the markers across files using NCBI build 37. For each result file, a given marker was excluded in case:

1. The combination of chromosome and base-pair position could not be uniquely linked to the HapMap Phase II CEU panel.
2. The marker had missing or incorrect values. Specifically,
    a. the effect allele and other allele were missing,

b. the association *p*-value was missing or outside the unit interval,
c. the effect estimate was missing or reported to have infinite magnitude,
d. the standard error (SE) of the effect estimate was missing, negative, or infinite,
e. the allele frequency was missing or outside the unit interval,
f. the sample size was not reported, or zero or below,
g. the reported callrate was outside unit interval,
h. the reported imputation quality was negative, and
i. the reported imputed dummy was not binary.

3. The marker was not a SNP, not biallelic, non-autosomal, and/or monomorphic.
4. The sample size was below 30.
   This filter is to guard against spurious associations due to overfitting of the model.
5. The minor allele count was 6 or below.
   This filter is to guard against spurious associations with low-frequency SNPs in small samples. The risk of spurious associations has shown to be particularly high for SNPs that are extremely rare[7].
6. Minor allele frequency (MAF) was below 1%.
   For all the cohorts, we dropped SNPs with a MAF below 1%. For small cohorts we applied more stringent filters based on diagnostic tests and figures.
7. The SE of the effect estimate was greater than $100/\sqrt{N}$.
   Based on the approximation to the expected standard error by Winkler *et al.*[7], we calculated that an SE greater than $100/\sqrt{N}$ is at least 40% greater than the expected SE of the estimated effect of a SNP with a MAF of 1% for a trait with standard deviation of 10. Since in our analyses we only consider SNPs with MAF≥1% and traits with a standard deviation below 10, an effect estimate with an SE greater than $100/\sqrt{N}$ can be considered to be unreasonably large.
8. The R^2 of the marker with respect to the phenotype was greater than 10%.
   We excluded SNPs for which the estimated R^2 was greater than 10% (Supplementary Information in Rietveld *et al.*[79]) because such an R^2 would defy all upper bounds on reasonable effect sizes of SNPs.
9. The marker was imputed while imputation quality was missing.
10. The marker was imputed while imputation quality was below 0.4.
    For all the cohorts, we dropped imputed SNPs with an imputation quality below 0.4. For several cohorts we apply more stringent filters based on diagnostic tests and figures.
11. The callrate was below 95%.
12. The SNP was genotyped and not in Hardy-Weinberg Equilibrium (HWE).
    We excluded genotyped SNPs if they fail the HWE chi-squared test. Violation of HWE will lead to lower chi-squared *p*-values as sample size increase, the threshold is therefore sample-size dependent. We applied an HWE *p*-value threshold of 10^{-03} in case $N < 1{,}000$, 10^{-04} in case $1{,}000 \leq N < 2{,}000$, 10^{-05} in case $2{,}000 \leq N < 10{,}000$, and no filter in case $N \geq 10{,}000$).

Diagnostic checks

For the SNPs remaining after applying the filters of steps 1 – 12, we generated five key diagnostic graphs:

1. Allele frequency (AF) plots. – to identify errors in allele frequencies and strand orientations.

The AF plot shows the expected AF (based on the HapMap II CEU2 reference panel or the 1000 Genomes Phase 1 European panel in case of 1000 genomes imputed data) versus the reported AF.

2. Reported P-values versus P-values of the Z-scores (PZ) plots – to assess the consistency of the reported P-values with respect to those implied by the effect estimates and the corresponding standard errors.
3. Quantile-Quantile (QQ) plots – to check for evidence of unaccounted population stratification.
4. Reported Standard Error versus Expected Standard Error (SE) plots – to assess whether the reported standard errors behave in line with the approximation of the expected standard errors provided by Winkler et al.[74] , implemented as a QC step by Okbay *et al*.[80]

These diagnostic plots were examined by two independent analysts. If problems were detected which could not be resolved by more stringent thresholds, we applied the following *ad hoc* filters (descending order in terms of frequency used).

1. MAF filters more stringent than the generic MAF filter (e.g., 5% instead of 1%).
2. Imputation quality filters more stringent than the generic filter (e.g., 0.8 instead of 0.4).
3. Filter on the absolute difference between expected (based on the HapMap II CEU2 reference panel or the 1000 Genomes Phase 1 European panel in case of 1000 genomes imputed data) and reported allele frequencies. This filter helps to remove clear outliers in the AF-plots (e.g., strand-ambiguous SNPs that are likely to have been reverse-coded).
4. Filter on the absolute difference between the reported log(*P*-value) and the log(*P*-value) derived from the report Z-score. This filter helps to remove clear outliers in the PZ-plots. Such outliers can arise when software such as SNPTEST[13] switches to another estimation method, for reasons such as poor convergence of the estimates.

For a list of the filters used per cohort, per association file, see Supplementary Table 27, which reports the total number of markers prior and post-QC when applying the described generic and specific filters, for each set of association results.

The AF plots for ABCFS (*N*=410 for AFB and NEB) shows a strong anti-diagonal that persists when considering only genotyped markers, implying that reverse-coded SNPs are likely to have been used for imputation, thereby yielding poorly imputed SNPs. Consequently, we exclude the ABCFS result files from the meta-analyses. In addition, for Longenity (*N*=285 for AFB and *N*=352 for NEB) many SNPs have far greater standard errors

for the effect estimates than expected, as well as callrates substantially below 95%. When applying QC to Longenity, only several hundreds of SNPs are left after QC. Consequently, we also exclude Longenity results from the meta-analyses.

2.6 Meta analyses

Cohort association results (after applying the QC filters) were combined using sample-size weighted meta-analysis, implemented in METAL.[81] Sample-size weighting is based on Z-scores and can account for different phenotypic measurements among cohorts.[82] The two QC centers agreed in using sample-size weighting to allow cohorts to introduce study-specific covariates in their cohort-level analysis. Only SNPs that were observed in at least 50% of the participants for a given phenotype-sex combination were passed to the meta-analysis. SNPs were considered genome-wide significant at *P*-values smaller than 5×10^{-08} (α of 5%, Bonferroni-corrected for a million tests. The meta-analyses were carried out by two independent analysts. Comparisons were made to ensure concordance of the identified signals between the two independent analysts. The PLINK clumping function[83] was used to identify the most significant SNPs in associated regions (termed "lead SNPs").

The total sample size of the meta-analysis is *N*=251,151 for AFB pooled and *N*=343,072 for NEB pooled. Although considered to be separate from our main pooled results, we also performed separate meta-analyses for

- AFB women (*N*=189,656),
- AFB men (*N*=48,408),
- NEB women (=225,230),
- NEB men (*N*=103,909)

The sex-specific results are discussed in more detail in Supplementary Note, Section 5. To understand the magnitude of the estimated effects, we used an approximation method to compute unstandardized regression coefficients based on the Z-scores of METAL output obtained by sample-size-weighted meta-analysis, allele frequency and phenotype standard deviation. Further details of the approximation procedure are available in the Supplementary Information of Rietveld et al.[79]

Figure S2.1.1. to Figure S2.13.2 contains the forest plots and regional association plots of all genome-wide significant SNPs, the latter created by LocusZoom plots.[84] The forest plots provide a visualization of the effect size estimates for each cohort and the summary meta-analysis (red rectangle) in addition to the 95% confidence intervals. As would be expected, small cohorts have larger confidence intervals. LocusZoom plots provide a graphic depiction of the local association results and include information about the locus, the location and orientation of the genes it includes, LD coefficients and the local estimates of recombination rates.

3. BIVARIATE AND CONDITIONAL ANALYSIS OF THE TWO FERTILITY-RELATED TRAITS

As joint analysis of correlated traits may boost power for mapping functional loci, we applied a recently developed multi-trait analysis method[85] to test the association between each variant and the two correlated traits AFB and NEB simultaneously using multivariate analysis of variance (MANOVA). The analysis was performed based on the genome-wide meta-analysis summary statistics of each single trait. The joint analysis did not reveal additional genome-wide significant loci (λ=0.995), however, such bivariate analysis, accounting for the correlation between the two phenotypes, improved the strength of two signals on chromosomes 1 and 5, indicating possible pleiotropic architecture between the AFB and NEB (Supplementary Figure 30).

The analysis also provides a conditional association test of the genetic effect of each variant on AFB including NEB as a covariate, and that on NEB including AFB as a covariate. The conditional analysis also did not reveal additional genome-wide significant loci (Supplementary Figure 31). Nevertheless, adjusting for NEB eliminated the three genome-wide significant loci on chromosomes 1, 2 and 6 for AFB, and adjusting for AFB eliminated the two genome-wide significant loci on chromosomes 1 and 14 for NEB, which may indicate underlying pleiotropic effects on both traits across these loci.

4. TESTING FOR POPULATION STRATIFICATION

Population stratification can severely bias GWAS estimates for causal variants and lead to false positives. This can occur if a particular variant of a SNP is more common in a particular subpopulation and if there are mean differences in the phenotype of interest between subpopulations due to factors that do not involve that SNP. As described in Supplementary Note Section 2, all cohorts in the GWAS of AFB and NEB included the top principal components[78] in their analyses to account for population stratification. Even despite this inclusion, residual stratification could still remain and affect the results.

To test the extent of this problem, we used two methods to assess if our GWAS results for AFB and NEB exhibit signs of population stratification. First, we used the LD Score intercept method described in Bulik-Sullivan et al..[86] Second, we conduct a series of individual and within-family (WF) regressions using polygenic scores (PGS) as predictors[87–89] on a dataset of DZ twins (STR and TwinsUK). Within-family regressions are based on family differences in PGS for AFB and NEB and are therefore are not affected by population stratification. We compare the coefficients of individual and WF regression using different p-value thresholds for the construction of PGS. Polygenic scores are based on independent results (i.e. meta-analysis results excluding STR and TwinsUK). Additional information on how we computed our PGS are available in Section 7 of the Supplementary Note.

4.1 LD Score Intercept Test

The LD Score intercept test uses GWAS summary statistics for all measured SNPs. LD Score regression is a method that can disentangle inflation in the chi-square statistics that is due to a true polygenic signal throughout the genome from inflation that is due to confounding biases such as cryptic relatedness and population stratification. The inflation due to a true polygenic signal impacts the slope of the LD regression, whereas inflation due to population stratification and other confounding biases affects the intercept of the regression.

We used the LDSC software[86,90] to estimate the intercepts in LD Score regressions with the summary statistics of our GWAS of: (i) AFB (pooled sample), (ii) NEB (pooled sample), (iii) AFB (women), (iv) AFB (men), (v) NEB (women), and, (vi) NEB (men). We estimated a separate LD Score regression for each of the phenotypes using the summary statistics from the meta-analyses based on all available data.

For each phenotype, we used the "eur_w_ld_chr/" files of LD Scores computed by Finucane et al.[91] available on https://github.com/bulik/ldsc/wiki/Genetic-Correlation. These LD Scores were computed with genotypes from the European-ancestry samples in the 1000 Genomes Project using only HapMap3 SNPs. Only HapMap3 SNPs with MAF > 0.01 were included in the LD Score regression.

Because genomic control (GC) will tend to bias the intercept of the LD Score regression downward, we did not apply GC to the summary statistics we used to estimate the LD Score regression. Furthermore, we excluded the deCODE cohort from the data for the estimation of the LD Score intercept for AFB and NEB, since the cohort-level regression estimates for deCODE did not directly correct for the high level of relatedness in the sample (their standard procedure is to apply GC). Our intercept estimates from the LD Score regressions are thus unbiased measures of the amount of stratification there is in the data (excluding deCODE) that we used for the GWAS of each phenotype.

Supplementary Note Figures 4.1 and 4.2 show LD Score regression plots based on the summary statistics from the GWAS of AFB, and NEB. For AFB, we estimated a LD Score intercept of 1.0216 (SE=0.008) and for NEB, 1.009 (SE = 0.006). In all six cases, the intercept estimates are not significantly different from 1. By comparison, the mean χ^2 statistics for all the SNPs in the LD Score regressions are 1.239 for AFB and 1.141 for NEB. Under the null hypothesis that there is no confounding bias and that the SNPs have no causal effects on the phenotypes, the mean χ^2 statistics would be one, thus mean χ^2 statistics greater than one indicate that some SNPs are associated with the phenotypes. These estimates imply that about 9% of the observed inflation in the mean χ^2 statistics for AFB and about 6% of the

inflation for NEB is accounted for by confounding bias (due to relatedness, or other confounds) rather than a polygenic signal.

As described in Section 2 of the Supplementary Information, we applied the standard single GC correction to produce our main estimates. Once a single GC is applied, the LD score regression estimates indicate negligible confounding bias due to population stratification. The LD score intercept for AFB is 0.9618 (SE= 0.0077) and for NEB 0.9763 (SE=0.0068). We can therefore conclude that the amount of inflation in our final results due to confounding bias is likely to be negligible.

4.2 Statistical Significance of the Polygenic Scores in a WF regression

To test the robustness of our all-SNP polygenic scores calculated with a set of SNPs meeting several different threshold P-values (5e-08, 5e-07,5e-06, 5e-05, 5e-04, 5e-03, 5e-02, 5e-01, all SNPs), we estimated WF regressions of AFB and NEB on each polygenic score in samples that are independent from those used to construct the scores. For each WF regression, we also compared the estimated coefficient on the polygenic score to the corresponding coefficient from individual-level regression.

For both the individual-level and WF regression, we standardized NEB and AFB on birthyear, birthyear squared, birthyear cubic, sex and the first 10 PCAs[a]. Our regressions are based on 7,944 twin couples for AFB and 9,220 twin couples for NEB. Supplementary Note Figures 4.1, 4.2 and Supplementary Tables 30, 31 report the results.

The regression analyses show that WF regression coefficients for both AFB and NEB are statistically different from zero when the p-value threshold is sufficiently far from zero. When including all SNPs, both coefficients for AFB and NEB are larger than zero, confirming that the GWAS analyses uncovered true polygenic signals. Overall, these results indicate a minimum effect of population stratification and the existence of polygenic signals.

[a] Details on the construction of polygenic scores is available in section 6 of the Supplementary Note.

5. SEX-SPECIFIC GENETIC EFFECTS IN HUMAN REPRODUCTIVE BEHAVIOR

Sex-specific genetic effects have been proposed as an important source of variation for complex human traits.[92,93] For this reason we also ran sex-specific GWAS meta-analyses for both AFB and NEB and examined the genetic overlap among sexes using LD score bivariate regression and GCTA. Sex-specific effects refer to large differences in average phenotypes or biological processes known to differ between the sexes (e.g., hormonal effects). Since AFB and NEB are not only biological but also socio-behavioral phenotypes, it is likewise important to make a distinction between sex- versus gender-specific effects. Sex refers to biological differences between males and females, which often have their underpinnings in human reproduction.[94] Gender refers to the socially constructed differences between men and women that may give rise to particular behavioral outcomes (e.g., gender-specific social norms regarding alcohol consumption or occupational choice). There is growing evidence that biological (sex) and social (gender) processes are interrelated, which in turn impacts the phenotypes we are examining.[95] Although we recognize the importance of these distinctions, it is beyond the scope of the current study to disentangle sex- versus gender-effects. Rather in this section, we emphasize similarities and differences in the sex-specific GWAS results and examine the sex-specific genetic overlap of these traits.

There are several key sex-specific differences in AFB and NEB. Women in contemporaneous populations have a comparatively lower age at first birth than men, which is attributed factors such as the persistent age gap between partners.[96] Fecundability is strongly influenced by sex-specific hormonal processes and gender-specific diseases. Sex can modify both penetrance and expressivity of a wide variety of traits.[97,98] Sex-genotype interactions can also theoretically act to maintain genetic variation in a population.[99] Sexual antagonism, which is the existence of opposite genotypic effects among sexes, has been often theorized as one of the possible explanations for genetic differences in fertility.[100] In other words, particular genes might influence men and women differently and could thus still be transmitted to the next generation. Genes that contribute to the fecundability of men may therefore be inherited via women's lineage and those for women via men's lineage.[101]

5.1 Sex-specific GWAS meta-analyses for AFB and NEB

In addition to the pooled GWAS results presented in the main text, we also ran sex-specific GWAS meta-analyses for AFB and NEB. The sample size for sex-specific analysis is: AFB women, N=189,656; AFB men, N=48,408; NEB women N=225,230; NEB men N=103,909. Our results indicate 6 genome-wide significant ($P<5x10^{-08}$) independent SNPs for AFB women and 1 genome-wide significant independent SNP for NEB men. We do not find any genome-wide significant loci for AFB men and NEB women. Among the 6 hits for AFB women, 5 are also significant in the AFB pooled analysis, while 1 hit on chr8 (rs2721195; chr8: 145677011) is specific for women. We find a single independent SNP for NEB men (rs13161115; chr5:107050002) that reaches genome-wide statistical significance (P-value$<5x10^{8}$), which is not significant in the NEB pooled analysis. Supplementary Figure 34 shows the Miami plots for AFB and NEB sex-specific analyses. Supplementary Figure 35 depicts the QQ plots of men and women's meta-analyses for AFB and NEB. The figure shows a noteworthy departure from the null hypothesis of no statistical association, in particular for the analysis of AFB women.

Table 1 (in the main text) shows the sex-specific signals respectively for AFB and NEB. The effects of all significant hits in AFB have the same direction for both men and women. The single locus found in NEB men (rs13161115) has an opposite effect on NEB for women, although the p-value associated with its effect size in NEB for women does not reach statistical significance.

5.2 Genetic overlap among sexes using LD score bivariate regression

We used LD score bivariate regression[8] to estimate the genetic correlation among men and women based on the sex-specific summary statistics of AFB and NEB meta-analysis results. For each phenotype, we used the "*eur_w_ld_chr/"* files of LD Scores computed by Finucane et al. and made available on https://github.com/bulik/ldsc/wiki/Genetic-Correlation. These LD Scores were computed with genotypes from the European-ancestry samples in the 1000 Genomes Project using only HapMap3 SNPs. Only HapMap3 SNPs with MAF>0.01 were included in the LD Score regression. Our estimates indicate a genetic correlation of r_g=0.86

(SE=i0.052) among sexes for AFB and r_g=0.97 (SE=0.095) for NEB. These results indicate a large genetic overlap among sexes for both AFB and NEB, which is statistically different from zero. We additionally test whether these genetic correlations support the null hypothesis of complete genetic overlap among sexes (r_g=1). We reject this null hypothesis for AFB, indicating sex-specific genetic variants for AFB. We do not find any evidence of sex-specific signals for NEB.

5.3 Genetic overlap among sexes using GCTA

We additionally estimate the degree of genetic overlap among sexes using Genomic-Relatedness-Matrix Maximum Likelihood (GREML)[46] on six cohorts for which we have direct access to genotypic data.[46,47,102–104] For the GREML analyses, we combine data from six cohorts: HRS, EGCUT, QIMR Lifelines Cohort Study, TwinsUK and STR (N_{women}=20,966; N_{men}=17,024, see Supplementary Table 33 for descriptive statistics). We used GCTA[46] to construct a Genome-wide Relatedness Matrix (GRM) $\boldsymbol{A^{n\times n}}$ and estimate the models. For quality control (QC), we included in the analysis only HapMap3 SNPs with an imputation score larger than 0.6. We additionally excluded SNPs with a missing rate larger than 5%, MAF lower than 1% and which failed the Hardy-Weinberg equilibrium test for a threshold of 10^{-06}. We applied these QC steps for each cohort and repeated again on the merged dataset. After QC, 847,278 SNPs could be utilized to estimate the GRM between individuals.

5.4 Bivariate GREML analysis

First, we fit a bivariate GREML model as proposed by Lee et al.[104] treating the fertility traits of men and women as different traits.[102] To account for potential country heterogeneity, we estimated genetic variation from within cohorts only ($\sigma^2_{g\_wc}$), setting the GRM between individuals from different cohorts equal to zero.[50] This allows us to avoid the potential bias due to differences in allele frequency across different countries. The GRM can be depicted as a block matrix composed by six within-cohort GRMs ($\mathbf{A}_{\boldsymbol{g_{wc}}}$) containing only values for pairs of individuals within cohorts.

The variance-covariance matrix of the bivariate model is shown as:

$$\boldsymbol{V}\begin{bmatrix}\boldsymbol{f_{men}}\\ \boldsymbol{f_{women}}\end{bmatrix}=\begin{bmatrix}\boldsymbol{A_{wc\_men}}\sigma^2_{g\_wc\_men}+\mathbf{I}\sigma^2_{e\_wc\_men} & \boldsymbol{A_{wc\_men\_women}}\sigma^2_{g\_wc\_men\_women}\\ \boldsymbol{A_{wc\_men\_women}}\sigma^2_{g\_wc\_men\_women} & \boldsymbol{A_{wc\_women}}\sigma^2_{g\_wc\_women}+\mathbf{I}\sigma^2_{e\_wc\_women}\end{bmatrix}$$

whereas $\boldsymbol{f_{men}}$ **and** $\boldsymbol{f_{women}}$ are vectors of length $N_{men}\ and\ N_{women}$ of fertility phenotypes (NEB or AFB), with N being the respective sample size of the subsets, $\boldsymbol{A_{wc\_men\_women}}$ is the within population GRM for all individuals, $\boldsymbol{A_{wc\_men}}$ is the within cohorts GRM for men, and $\boldsymbol{A_{wc\_women}}$ for women. The parameter $\sigma^2_{g\_wc\_men}$ is an estimate of the genetic variance component for men and $\sigma^2_{g\_wc\_women}$ and $\sigma^2_{g\_wc\_men\_women}$ the genetic covariance across sexes. **I** is the identity matrix, and $\sigma^2_{e\_wc\_women}$, $\sigma^2_{e\_wc\_men}$ the respective, sex-specific residual variances within cohorts. We present the variance components standardized for the phenotypic variance σ^2_p. The correlation of the genetic factors are estimated as:

$$r_{\sigma^2_{g\_wc\_men\_women}}=\sigma^2_{g\_wc\_men\_women}/\sqrt{\sigma^2_{g\_wc\_men}*\sigma^2_{g\_wc\_\mathrm{women}}}$$

We find significant heritability for NEB and both sexes $\sigma^2_{g\_wp}/\sigma^2_P$ = 0.13 (SE=0.057, P=0.01) for men, and 0.08 (SE=0.04, P=0.01) for women (see Supplementary Table 34 for full results). This means that around 10% of the variance in NEB is explained by common SNPs for both sexes. The estimated genetic correlation across sexes is 0.98 (SE=0.44) and a likelihood ratio-test against a perfect genetic correlation across sexes has a p-value of 0.5. We therefore cannot reject the null-hypothesis that genetic effects are the same across sexes.

For AFB we find a very similar pattern of sex specific SNP-based heritabilities of around 0.10 and a genetic correlation of 1.00 (SE=0.67, P=0.5 when testing against 1). These results also cannot reject the null-hypothesis that genetic effects on AFB are the same across sexes.

5.5 Analysis of differences between sample and effect sizes

Table 1 in the main text did not include the Ns of the sex-specific analyses. It is, however, important to place the p-value of women and men in context and clarify why the effect size for some loci is similar in men and women but the p-value is not. This could reflect a difference in sample size, or it may reflect a difference in variance. Supplementary Table 32 shows all of the sex-specific sample sizes, p-values, z-scores and the p-value differences

between males and females by each SNP. It indicates sex-specific effects and a statistical test showing the differences between effect sizes.

The statistical test is based on the differences between male and female Z-scores:

$$Z_{diff} = \frac{\frac{Z_1}{\sqrt{N_1}} + \frac{Z_2}{\sqrt{N_2}}}{\sqrt{\frac{1}{N_1} + \frac{1}{N_2}}} \sim N(0,1)$$

Supplementary Table 32 reports the P-value differences of this Z-score test. Despite the fact that p-values differ among the sexes, it seems plausible that the differences are mainly due to variation in sample size and not attributed to different effect sizes. Our results show that the only locus that has a statistically different effect between men and women after taking into account the number of test conducted is *rs13161115* in chromosome 5, where the effect is significant only in men and the direction of the effect differs among sexes.

5.6 Discussion

Sex-genotype interactions and sexual antagonistic effects may affect the transmission of traits across generations and has been proposed as a possible source of genetic variation in fertility traits.[101] Fecundability is strongly influenced by sex-specific hormones and infertility causes differ between men and women.[105] Our results show little differences in the genetic architecture of the fertility traits (AFB, NEB) of our study between men and women. Out of 12 independent loci for AFB and NEB, only two have a sex-specific effect. Moreover, all the signals found for AFB and two out of three signals in NEB, have a consistent direction across the sexes. We found a high genetic correlation among men and women for both AFB and NEB, both using LDscore bivariate regression and GREML bivariate analysis. This suggests that most of the genetic effect of fertility due to common SNPs is shared across sexes. However, using LDscore regression, we reject the null hypothesis of r_g=1 for AFB (P=0.007). A possible explanation of why we have not found more evidence for sex-genotype interactions may attributed to the fact that we analyzed only common variants and that we restrict our analysis to autosomal chromosomes. Moreover, our sex-specific meta-analysis may be underpowered to discover sex-specific loci.

When we compare Table 1 and 2, we note that in addition to the chr 5 locus for NEB, the chr

2 locus for AFB also shows a discrepancy between a sex-specific effect in the GWAS (women only) versus the (known) function of a candidate gene (AFF3). It would be premature to draw any firm conclusions since little is known about the role of AFF3 (chr 2) and EFNA5 (chr 5) in reproduction. For a substantial number of loci there are differences in the p-value between men and women, but the effect size suggests the association is present in both sexes. Only four loci seem to have a convincing null effect in men (rs1160544, rs10056247, rs2721195) or women (rs1316111). We would encourage functional follow-up studies on these points to further our understanding of human reproduction.

6. POLYGENIC SCORES PREDICTION

We performed out-of-sample prediction using cohorts for which we have direct access to genotypic data. We calculated polygenic scores for AFB and NEB, based on GWA meta-analysis results and used regression models to predict the same phenotypes in four independent cohorts: HRS, Lifelines, STR and TwinsUK. We ran ordinary least-squares (OLS) regression models and report the R^2 as a measure of goodness-of-fit of the model. In addition, we tested how well our polygenic scores for NEB could predict childlessness at the end of the reproductive period (using age 45 for women and 55 for men). Since age at first birth is observed only in parous women, we adopt an additional statistical model to account for censoring and selection. Finally, we also tested the predictive value of our polygenic scores for AFB for age at menarche (using TwinsUK) and age at menopause (using Lifelines).

6.1 Linear polygenic scores for AFB and NEB

We ran meta-analyses of the pooled AFB and NEB phenotypes, excluding each of the independent cohorts. Using these summary statistics, we constructed linear polygenic scores using the effect sizes from the original meta-analysis.[1] We constructed all scores using the software PLINK and PRSice[2,3] based on best call genotypes imputed to 1000G. For each phenotype, we calculated nine different scores using different p-value thresholds: 5e-08, 5e-07, 5e-06, 5e-05, 5e-04, 5e-03, 0.05, 0.5 and 1. Results are clumped using the genotypic data as a reference panel for LD structure.

We first regressed each phenotype on birthyear, its square and cubic to control for nonlinear trends in fertility, and the first 10 principal components, following the analysis plan distributed to the cohorts. If the cohort included both men and women, we included sex as a covariate in the regression models. Next, we regressed the residuals from the previous regression on the polygenic score. We performed a set of Ordinary Least Squares (OLS) regressions where we calculated R^2 as an indicator of goodness-of-fit of the regression model. For twin studies (STR and TwinsUK), we included only one MZ twin in the analysis and used clustered standard errors at the family level. To obtain 95% confidence intervals (CI) around the incremental $R^{2's}$, bootstrapping was performed with 1,000 repetitions.

The results of the polygenic score analyses are depicted in Supplementary Figure 2. The sample-size-weighted mean predictive power of the AFB score constructed with all SNPs is 0.9%, while the NEB score predictive power is 0.2%.

6.2 Linear polygenic scores for infertility

We used the score for NEB in an additional analysis to predict the probability to remain childless at the end of the reproductive period. Despite its limited predictive power for number of offspring, our analysis shows that an increase of one standard deviation of the polygenic score is associated with a decrease of around 9% in the probability to remain childless for women, with no significant differences among men (see Supplementary Table 21). The results are consistent across different cohorts.

6.3 Additional statistical models for censoring and selection

There are two limitations when studying the genetic determinants of AFB. The first is that this measurement is assessed only for men and women who ever became parents and does not take into consideration that a proportion of respondents are still at risk of having a child (i.e., did not have a child yet by the date of the interview) or will remain childless. This problem is commonly referred in the statistical literature as ‘right censoring’, since the outcome is not observed for all respondents, despite the fact that part of the respondent are still ‘at risk’ of

experiencing childbirth.[106] The second problem is statistical selection. Individuals with a measurement of AFB may be genetically different from individuals who remain childless. If childless individuals are different from the general population, the association results on AFB may be biased by selection problems. To investigate these two issues further, we estimated additional statistical models.

To control for right-censored data, we estimated semi-parametric Cox regression models[4] in which we estimate the effect of the polygenic score (PGS) on increasing the hazard of having a child conditional at each age. In other words, it is a model that estimates the impact of AFB PGS on yearly AFB, which will allow us to assess whether an increase in the AFB PGS is associated with a reduced risk of childbearing at each yearly age interval. This class of models takes into account censoring and is widely used to study fertility timing.[107] Our results show that the calculated PGS for AFB based on all SNPs is associated with an increased risk of childbearing at any age. The median AFB for men in the pooled sample is 28 and 26 for women. The hazard ratio of the PGS for AFB is 0.92 for women and 0.97 for men. This means that an increase of one standard deviation in the PGS is associated with an increase of 8% of AFB for women and 3% for men. Results for different cohorts and sex are depicted in Supplementary Table 22. Since this is a survival model that handles right-censoring (i.e., that the event of AFB did not occur by the observation time), the interpretation is that an increase in one standard deviation of the AFB PGS is associated with a reduction of 8% and 3% respectively for women and men in the hazard ratio of reproduction.

To control for selection, we estimated bivariate Heckman selection models in which we estimate the probability to be 'eligible' or at risk for AFB in a two-step procedure. Since we are interested in possible genetic differences among men and women who ever had children with respect to childless individuals, we used the PGS for NEB to model the probability to be at risk for AFB. The results from the Heckman selection models indicate slightly lower coefficients than OLS regression models but no substantial differences (see Supplementary Table 35 for details).

6.4 Linear prediction of age at menarche and age at menopause using AFB linear score

As an additional test, we examined whether the aforementioned PGS scores for AFB and NEB can predict related fertility traits such as age at menopause and age at menarche. We used the age at menopause measurement included in the Lifelines cohort. Age at menopause is measured with the question: "At which age have you had your last menstrual period?*"* We excluded women from the sample who reported to have had their last menstruation before age 30 or after age 60. The median age at natural menopause (ANM) in the sample is 45. Our results show that the PGS for AFB is associated with a later ANM. Since a substantive proportion of the sample of women in Lifelines is still in the pre-menopausal period, we estimated a proportional hazard model (Cox regression) in which we estimate ANM as a function of PGS for AFB. Our estimates indicate that having higher predisposition for AFB is associated with a later ANM. The hazard ratio estimate 0.97 indicates that an increase of one standard deviation of the PGS for AFB is associated with a decrease of ANM of about 3%. We used TwinsUK to model age at menarche. Our estimates indicate that an increase of one standard deviation on the PGS of AFB is associated with an increase of 0.06 years on age at menarche.[5] Results are depicted in Supplementary Table 23.

6.5 Association of menopause variants with AFB

We also examined whether menopause variants are associated with AFB. We calculated a PGS of age at menopause based on the recent GWAS results from Day et al. (2015)[108] and applied them to LifeLines and TwinsUK. The results for this analysis can be found in Supplementary Table 36 and shows no predictive power of the menopause genotype on AFB. This is consistent with the lookup exercise presented in S7.2, where none of our loci were significantly associated with age at Menopause. There might be several reasons why the LD score regression indicates a positive genetic correlation but we do not find evidence for specific loci. First, one or both of the studies may be underpowered and thus unable to identify a sufficiently large number of variants. Second, the correlation between the two traits may be spurious and mediated by other traits (e.g., age at menarche). We agree that it would be very interesting to pursue this in further research.

6.6 Discussion: The predictive power of polygenic scores

We acknowledge that the predictive power of the polygenic scores created from a meta-analysis of over 60 GWASs is only a fraction of what has been found in previous twin and family[1] and even GREML studies.[38] Several reasons have been noted for this 'missing heritability' problem,[109] including non-additive genetic effects,[49] epistatic effects,[110] rare variants and inflated estimates from twin studies due to *differential sharing of environmental factors in monozygotic and dizygotic twin pairs*.[111] Other factors that can explain the lower magnitude of effects are also plausible. Firstly, as we elaborate in Section S1.5, human reproductive behavior is not only biological, but also strongly related to environmental factors, and we should therefore not expect to find large independent genetic effects. We do not expect the PGS score to explain part of the variance attributable to environmental factors (i.e., the C and E in twin studies), but rather argue that these environmental factors are likely much stronger than genetic factors for these behavioral outcomes. As argued recently elsewhere,[39] it is vital to note that deep genetic analyses need to be united with strong and direct phenotypic measures. Although AFB and NEB are robustly measured, they inherently include a mix of voluntary (choice) and involuntary (infertility) measures. To overcome this problem, future innovations must unite rich genetic data with equally rich and precise phenotypic data collected precisely and continuously over several generations.

A second factor is that when studying phenotypes with behavioral component, GWAS discoveries are potentially limited by heterogeneity across birth cohorts and populations (e.g., countries) and particularly prone to gene-environment interaction. Fertility behavior has been demonstrated to be strongly environmentally determined and modified (e.g., by the introduction of effective contraception).[18] Although we examine gene-environment interaction across birth cohorts in Sweden in the Supplementary Note (section 10.1), in future research we will explore whether gene-environment interaction plays a role across birth cohorts and countries, with preliminary evidence suggesting that this is the case.[112] This is in line with recent research that has shown cohort differences in the genetic influence on smoking over time.[113]

7 GENETIC CORRELATIONS

7.1 Estimating genetic overlap using LD score regression

The estimates of the LD score regression reported in the main text was based on the LD-score regression method, which was developed by Bulik-Sullivan et al. (2015).[90] Here we describe in more detail how these estimates were computed and the genetic correlation we estimated between AFB and NEB and 27 publicly-available GWAS results (Supplementary Table 25 and graphed in Figure 3 in the main text). We focus on infertility traits, developmental traits, anthropometric traits, neuropsychiatric conditions and selected behavioral traits. LD score regression works even in the presence of sample overlap and only requires summary statistics and a reference panel from which to estimate SNP's "LD score", which measures the amount of genetic variation tagged by a SNP.

The approach requires GWAS summary statistics for all SNPs in our GWAS and a reference sample from which the LD can be estimated in order to estimate the LD score regression.[86] The method is written formally based on the following relationship:

$$E\left[z_{1j}z_{2j}\right] = \frac{\sqrt{N_1N_2}}{\mathrm{M}}\ell_j\rho_g + intercept,$$

Where z_{kj} is the z-score of SNP *j* from the GWAS of trait *k* (*k*=1,….,20), N_k is the sample size of the GWAS of trait k, $\ell_j$is the LD Score of SNP *j*, *M* the number of SNPs included in the GWAS, ρ_g the genetic covariance between traits *1* and *2*, with the regression intercept represented by *intercept*. The slope from the regression of $\hat{z}_{1j}z_{2j}$ on $\sqrt{N_1N_2}\ell_j$ can be used to estimate the genetic covariance between the two traits. We are also able to estimate the heritabilities of the two traits, h_{g1}^2 and h_{g2}^2 from the univariate LD score regressions of traits 1 and 2. It therefore follows that an estimate of the genetic correlation is:

$$\hat{r}_g = \frac{\widehat{\rho_g}}{\sqrt{\hat{h}_{g1}^2\hat{h}_{g2}^2}}$$

We use the file of LD scores computed by Finucane et al.[91] using genotypic data from a European-ancestry population (eur_w_ld_chr). LD Scores are computed with genotypes from the European-ancestry samples in the 1000 Genomes Project using only HapMap3 SNPs. We additionally follow the common convention of restricting our analyses to SNPs with MAF > 0.01, thus ensuring that all analyses are performed using a set of SNPs that are imputed with reasonable accuracy across all cohorts that contributed towards meta-analyses.

The standard errors (SEs) produced by the LDSC python software package uses a block jackknife over the SNPs. This influences the interpretation. Conventional standard errors are interpreted as measuring the variability of the estimate holding the covariates constant, but drawing on a new set of individuals. In this technique, SEs are interpreted as the variability of the estimate holding the sample constant, but drawing a new set of SNPs.

7.2 Estimating the genetic correlation between AFB and NEB

The negative relationship of late AFB with lower NEB[7,10,114] is well-established and consistent in advanced societies. Behavioral genetic models, based on twin or family studies show that this correlation is partially genetic, suggesting that natural selection favored a younger age at first birth over the Twentieth century.[1,38,115]

A recent study on genetic basis of fertility traits using molecular genetic data shows that common genetic variants influence NEB and AFB in a large sample of unrelated women.[38] Their results indicate a significant negative genetic correlation (r_g=–0.62, SE=0.27) between AFB and NEB. This finding implies that individuals with genetic predispositions for an earlier AFB had a reproductive advantage. We replicated the analysis of Tropf et al.[38] on a large sample of women from the Women General Health Study (WGHS, sample size N=40,120). We found a negative genetic correlation (r_g=–0.26, SE=0.13) between AFB and NEB. The results were limited to women and applied to a limited sample. We extend this work using LD score bivariate regression[86,90] on AFB and NEB on both men and women to identify the extent of cross-trait genetic correlation.

The LD score bivariate estimates indicate high negative correlation r_g=–0.66 (SE=0.03, p-value=$1.03x10^{-102}$) between AFB and NEB. This result is consistent both in men and women and is in line with the phenotypic correlation. Genetic correlation of fertility traits among women is slightly higher (r_g=–0.66, SE=0.04) than men (r_g=–0.58, SE=0.07). Overall these results show a considerable genetic overlap between NEB and AFB (as found in section 3). However, since the genetic overlap is statistically different from 1 for both men and women, these results indicate the existence of trait-specific genetic components.

7.3 Results: phenotypic correlations with human reproductive behavior

As discussed in the main text, we used information from 27 publicly available GWAS results to examine phenotypic correlations between AFB and NEB (Supplementary Table 25 and Figure 3 in the main text). These included: nine developmental traits, some of which are directly related to the reproductive span (age at menarche,[116] age at menopause,[117] Tanner stage,[118] age at voice breaking for males,[119] polycystic ovary syndrome (PCOS),[120] age at first sexual intercourse,[23] DZ Twinning,[121] birth length,[122] birth weight[123]), four behavioral traits (years of education,[76,79] cigarettes per day,[124] ever smoked,[124] age onset smoking[124]), seven personality and neuropsychiatric traits (neuroticism,[125] openness, schizophrenia,[126] bipolar disorder,[127] subjective well-being,[80] Alzheimer's disease,[128] autism[129]), four cardiometabolic traits (LDL cholesterol,[130] triglycerides,[130] type 2 diabetes,[131] fasting insulin levels[132]), and three anthropometric traits (BMI,[133] height,[87] waist-hip ratio[134]).

As shown in Fig. 3 and Supplementary Table 25 (P-values in bold indicate Bonferroni correction (P-value<0.05/27=$1.85x10^{-03}$)), AFB is positively correlated with years of education, age at menarche, age at menopause, age at voice breaking, age at first sexual intercourse and adult height, while it is negatively correlated with PCOS, adult BMI and waist-hip ratio, triglycerides, diabetes and fasting insulin level. Once multiple testing is controlled for, years of education and age at first sexual intercourse are the only traits significantly correlated with NEB (P-value<$2.25x10^{-03}$), and the direction is negative for both traits.

7.4 Discussion

7.4.1 Human development

AFB was shown to be positively correlated with the development measures of age at menarche, age at menopause, age at voice breaking and age at first sexual intercourse. A later age of menarche (AOM) has been associated with subfecundity and infertility in adulthood. A recent large cohort study of 73,107 women[135] demonstrated that women who reached menarche later than 15 years (compared to a reference group of girls with an AOM at 13 years) had a higher risk of infertility. Women younger than 11 years at AOM had lower odds of subfecundity and all results remained significant also after adjusting for women's age of pregnancy. Some studies, however, have also found a significant relationship between early AOM with diminished functional ovarian reserve later in life among infertile women.[136] There is also evidence of a small increased risk of endometriosis associated with early AOM.[137]

Stolk et al. (2012)[138] linked age at menopause to genes implicated in DNA repair and immune function. A recent study reported genetic correlations indicating shared aetiologies in both sexes between the timing of puberty and BMI, lipid levels, type 2 diabetes and cardiovascular disease.[139] Fertility timing has been positively associated with age at menarche and age at first intercourse. Although previous research has largely focused on identifying genes related to menopause and menarche that mark the end the beginning and end of the reproductive career, it is also possible that observed fertility (AFB, NEB) influences the subsequent age at menopause and ovarian aging. Exploring these overlaps and associations would be an interesting area for future research.

Results from a genetic study of age at first sexual intercourse (AFS) linked AFS to variation in pubertal timing, but also personality characteristics related to high risk-taking and low neuroticism.[23] We examine the link with AFS and neuropsychiatric disorders in a later section (Section 7.4.5).

7.4.2 Cardiometabolic traits

Having more AFB-increasing alleles was also significantly associated with a lower genetic scores for triglycerides, Type 2 Diabetes and fasting insulin level. Pregnancy for women results in considerable alterations in the cardiovascular system.[36] Reproductive events are associated with alterations in blood lipids and blood pressure and may therefore influence determinants of coronary heart disease. As with diabetes, there are mixed findings regarding the link between age at birth, parity and coronary heart disease (CHD). Some studies have linked the number of children and CHD risk with the prevalence lowest among those with 2 children with a linear increase with each additional child.[22] These researchers have argued that it is not the pregnancy per se that has a biological impact but rather that the lifestyle risk factors associated with childrearing leads to obesity which in turn results in increased CHD in both sexes. Yet, they maintain the argument that biological responses of pregnancy may have additional adverse effects in women.

Other studies attempted to elucidate the mechanisms linking multiparity to cardiovascular disease demonstrating that repeated pregnancies induce long-term changes in cardiovascular regulation in women due to the changes in vascular compliance and endothelium-dependent vasoconstriction, which in turn increase the risk for CHD in multiparous women.[36] A recent study related early puberty timing to higher risks for both Type 2 Diabetes and cardiovascular disease.[27] It may be however, that just as with the studies on GDM (gestational diabetes mellitus) described shortly, retrospective and cross-sectional approaches may have limitations related to selectivity and unobserved confounding factors. A prospective study in the US found that a younger age at menarche was only weakly associated with CHD and that nulliparous women only had a slightly higher rate of CHD compared to parous women. They also found no change in the risk with an increasing number of births or any association with the age at first birth concluding that there is no clear link between reproductive history and risk of CHD.[140] Further research is required to establish whether there is a true *causal* link and underlying genetic and biological mechanisms to explain the association between reproductive history and cardiometabolic traits.

There does, however, appear to be a link with the cardiometabolic traits that we measure in this study with infertility. Total cholesterol, triglycerides, LDL cholesterol levels and fasting insulin levels have been shown to be statistically higher in groups with endometriosis

compared to controls.[141] Endometriosis is estimated to occur in 5-10% of premenopausal women with ~50% experiencing problems conceiving.[34] A recent study also revealed a link between endometriosis and obesity-related traits.[142] Other studies have also linked the impact of maternal cholesterol metabolism to ovarian follicle development and fertility.[143] The role of the low-density lipoprotein receptor in cellular metabolism in inhibiting human reproduction has likewise been established.[144] Others have linked metabolic syndrome, which is a compilation of symptoms such as a high BMI (obesity), type 2 diabetes, dyslipidemia, and hypertension with an increased prevalence of infertility in men.[145]

A wide body of research links reproductive history to Type 2 Diabetes. Early studies found that nulliparity and multiparity or grand parity (5 or more children) was associated with higher levels of fasting glucose and insulin levels among nondiabetic women.[146–148] Multiparity has been associated with higher risks of cardiovascular disease in both women and men[27,149,150] and higher insulin resistance and type 2 diabetes.[149,151] Other research found that high parity was associated with insulin resistance and type 2 diabetes, which even after adjusting for confounders (socioeconomic, higher obesity, inflammatory markers) grand parity is associated with a 27% increased risk for diabetes (95% CI, 1.02-1.57).[151]

It is essential to note, however, that early cross-sectional and retrospective studies did not control for age, body size or socioeconomic status. Later cross-sectional studies that controlled for the abovementioned factors, continue to produce highly mixed results (for a review see ref [152]). A key limitation is that many of the previous studies lack universal GDM (gestational diabetes mellitus) screening and did therefore not measure preconception glycaemia or glucose intolerance during pregnancy. A systematic review and meta-analysis demonstrated that women who had gestational diabetes had a seven-fold greater risk of developing Type 2 Diabetes.[152] This suggests that once GDM status is accounted for, the direct parity effect will be very small or null. One the other hand, unobserved conditions such as PCOS, obesity or insulin resistance could in fact cause infertility (nulliparity) which would in turn lead to an underestimation of the association.

Gunderson et al. (2007)[153] examined whether childbearing increased the incidence of Type 2 Diabetes after preconception glycaemia and gestational glucose intolerance were controlled

for. They concluded that childbearing did not elevate the incidence of diabetes among those without GDM (i.e., normal glucose tolerance during pregnancy). It was GDM rather that was associated with the highest risk of developing diabetes, which remained even after controlling for family history of diabetes, preconception glycaemia and obesity. Another study using GDM screening found that a woman's age remained a strong predictor even after adjusting for prior GDM history, mirroring the general historical increase in GDM (and related levels of obesity) across time in certain groups. A logistic regression analysis also showed that mother's age at birth (OR 95% CI per 5 years 1.6–1.8) was significantly associated with GDM. Parity was not significantly associated with GDM and had no effect on the GDM increase over time.[154]

7.4.3 Anthropometric traits

A considerable body of literature links anthropometric traits (such adult height, BMI and increasingly waist-hip ratio) with fertility timing and success.[133,155] Anthropological research argue that shorter women may have more reproductive success because of the trade-off between investing in energy in growth or reproduction.[156] Moreover, taller women appear to become fertile at a later age (e.g., age at menarche) than shorter women, and women who have children at an early age reach a shorter adult height, which may result in a negative relationship between women's height and reproductive success.[155,157] The relationship between men's height and fertility is more complex. One paper revealed a curvilinear association between men's height and number of children in a nationally representative sample of US respondents.[158] Men of average height appear to have a higher reproductive success than either short or tall men. The relationship between height and number of children in advanced societies is not always negative. A recent paper showed that in the Netherlands – the country with the highest average population height – the relationship is the opposite.[155] A possible mechanism through which height may affect fertility is sexual selection and assortative mating. There is a certain degree of homogamy in anthropometric traits among spouses, even after controlling for a variety of socio-economic traits.[159,160]

BMI and waist-hip ratio (WHR) is another area of research often linked with fertility success, particularly in couples seeking ART treatment.[161] Both a very low and a very high BMI have been found to delay both the timing and number of children in both men and women.[162]
Waist-hip ratio measures body fat distribution and serves as a more accurate predictor of metabolic consequences independent of overall adiposity. A study locating new loci for WHR also found that seven of the loci exhibited marked sexual dimorphism, or in other words, that the genetic loci that modulate fat distribution have a stronger effect on WHR for women than men, suggesting strong gene-by-sex interactions.[163]

7.4.4 AFB and educational attainment

As described already in detail in Supplementary Note Section 1.5, the strong relationship between AFB and years of education is not surprising, since educational attainment is associated with higher AFB and a lower NEB in most advanced societies.[54,164] As discussed previously, the study of the relationship between higher educational attainment and reproduction has been a central focus within demography and related social sciences.[7,10,58,114,165] The majority of the research demonstrates that achieving higher education (particularly of women) operates to postpone AFB. Other studies have shown that fertility postponement may be related to higher cognitive ability,[166] but additional research is required to separate cognitive scores from social environment (e.g., family environment, social class). Others have found that after controlling for age, physical maturity and mother's education, there is a significant curvilinear relationship with intelligence and early sexual intercourse with both very low and very high intelligence operating as a protective factor against early sexual activity.[167] Further careful research in this area would be necessary to understand the relationship.

7.4.5 AFB, personality and neuropsychiatric disorders

The results of the LD score regression did not find any significant association with neuroticism, openness, schizophrenia, bipolar disorder, well-being, Alzheimer's disease or autism, so we will only touch upon this topic briefly. Personality has been demonstrated to be predictive of fertility intentions[20,168] and the timing of childbearing.[169,170] The finding that AFB is negatively correlated with neuroticism has also been found in previous non-genetic

studies linking AFB to personality traits.[171,172] A bidirectional effect between fertility and psychological development has likewise been documented.[168,173] This may suggest that the interaction between genetic and environment factors could be interpreted as genetic influences on fertility that have an effects on both fertility behavior and psychological outcomes. Since personality, educational attainment and cognitive ability are largely formed before individuals enter into their childbearing years, it is plausible that personality and cognitive traits are likely causal and precede fertility variables.[174] A recent study also demonstrated a genetic overlap between schizophrenia and AFB, showing a U-shaped relationship. The study confirmed that the schizophrenia risk profile score significantly predicted the relationship between maternal age and risk of schizophrenia in offspring.[16]

7.4.6 Smoking behavior

The strong negative correlation of a lower genetic risk of smoking (less cigarettes per day, lower chance to have ever smoked and later age of onset smoking) with a later AFB could operate via two mechanisms. First, it is well established that cigarette smoking has a detrimental biological effect on ovarian function and spermatozoa. There is an established link of a longer time to conception and decreased fertility with the increasing number of cigarettes smoked per day.[175] Other studies have linked cigarette smoking to infertility such as problems with preimplantation[176], shrinking the size and quality of oocytes[177], and abnormal spermatozoa by decreasing sperm motility in smokers.[178] A second potential mechanism is that the earlier onset of smoking and higher number of cigarettes smoked per day is also highly stratified by socioeconomic status. Smoking and low socioeconomic status are often linked to other environmental risk factors and a higher co-morbidity for other diseases.[179] Smoking is thus often a marker for structural, health and material disadvantage in addition to being concentrated in groups with the lowest levels of education.[180]

7.4.7 Limitations of LD score regression genetic correlations

Although LD score regression is a powerful tool to identify possible relationships between traits, we acknowledge that it does not allow us to establish causal directions or relationships or to adjust for potential mediating factors. The relationship between many of the traits discussed in this section is highly complex with potential bi-directional mechanisms. Further

studies are required to explore these relationships and establish whether the genetic risk related to AFB and NEB are either partially or fully mediated by other factors.

URLs.

The LDSC software is available at the website: http://www.github.com/bulik/ldsc;
GWAS summary statistics are available at the following websites: PGC (psychiatric) summary statistics, http://www.med.unc.edu/pgc/downloads; GIANT (anthropometric) summary statistics, http://www.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files; data on birth length, birth weight, Tanner stages have been contributed by EGG Consortium and has been downloaded from www.egg-consortium.org.; data on glycaemic traits have been contributed by MAGIC investigators and have been downloaded from www.magicinvestigators.org; DIAGRAM (type 2 diabetes) summary statistics, http://www.diagram-consortium.org/; SSGAC (educational attainment) summary statistics, http://www.thessgac.org/.

8. LOOK-UP OF LEAD SNPS IN AFB GWAS FOR AGE AT MENOPAUSE AND AGE AT MENARCHE

Following the results on genetic overlap with other phenotypes we tested – in a quasi-phenotype replication setting – whether the SNPs strongly associated with AFB in women are empirically plausible candidates SNPs for age at menarche and age at menopause. Our results reported in the previous section (Supplementary Note, Section 7) indicate a strong genetic correlation between these traits, suggesting a common genetic basis of reproductive behavior and reproductive life span.

Here we use a two-stage approach that has been applied in other contexts.[80,181] Since we are only looking at phenotypes measured among women with menarche and menopause, we started our analysis from the meta-analysis results from the AFB sample of women. In the first stage, we conduct a meta-analysis of age AFB excluding the cohorts that were part of the meta-analysis of the phenotype we intend to replicate. This step reduces the risk of overlap between the AFB sample from which the candidate SNPs are drawn and the sample used for testing the other phenotypes. We merged these SNPs with the publically available association results on the most recent GWAS on age at menarche[116] and age at menopause[117] from the Reprogen consortium website[b]. We first merged the two association files and dropped SNPs that are not present in both the files. We aligned the alleles and the effects direction using the software package EasyStrata.[182] We then selected the independent SNPs with a p-value$<1x10^{-5}$, using the clump procedure in PLINK[83], using the same settings described in section SI.2 (1000Kb window and LD threshold of $R^2>0.1$) to identify the most significant SNPs in associated regions included in both files. We define "prioritized SNP associations" as those that passed the Bonferroni correction for the number of SNPs tested ($P=0.05/122=4.10x10^{-4}$, both in age at menarche and age at menopause).

Supplementary Figure 36 shows the QQplots of the leading SNPs for AFB on age at Menarche (panel a) and age at menopause (panel b). Our results identified three SNPs after

[b] Data downloaded in November 2015 from http://www.reprogen.org/data_download.html

Bonferroni-correction that can be used as good candidates for age at menarche. We do not isolate any clear “candidate SNP” for age at menopause. The three SNPs that we identified (rs9589; rs6803222; rs9858889) are all in Chromosome 3. Two of them (rs9589; rs6803222) lie in proximity (<500Kb) of rs2777888, which has been identified as the strongest signal in our AFB GWAS.

9. BIOLOGICAL ANNOTATION

9.1. Identifying potentially causal variants

We followed the post-GWAS pipeline reported by Vaez et al[183] to shed light on the genomic context of the 12 independent genome-wide significant SNPs (Table 1 of the main text).

***In silico* sequencing:** For *in silico* sequencing, we used the data of the 1000 Genomes Project phase3 release of variant calls. This data set is based on the 20130502 sequence freeze and alignments. We used version v5a (Feb. 20th, 2015), and included only the 503 subjects of European ancestry (accessed April 5, 2016)[184]. The Variant Call Format (VCF)[185] files for regions of 1 Mb at either side of each lead SNP were downloaded using the Tabix software package.[186] Then, the r^2 between the lead SNPs and all other bi-allelic SNPs within the corresponding 2 Mb area was calculated as a metric of linkage disequilibrium (LD) using the Plink software package (v1.07).[83] All SNPs in LD with any of the lead SNPs were then annotated by ANNOVAR software[187] (version 1 Feb 2016, accessed April 9, 2016). We also used Sorting Intolerant From Tolerant (SIFT)[188] and Polymorphism Phenotyping (PolyPhen)[189] prediction scores to characterize the damaging impact of the nonsynonymous SNPs on the corresponding proteins. These scores were obtained from Ensembl release 83 (accessed April 11, 2016).[190]

In silico pleiotropy analysis

To identify any other trait or outcome associated with these 12 independent loci, we used the publicly available data of the National Human Genome Research Institute (NHGRI) GWAS Catalog (Catalog of Published Genome-Wide Association Studies).[191] We checked for pleiotropic effects of all lead SNPs as well as their linked variants (revealed in the previous phase of *in silico* sequencing) on other complex traits or diseases identified in previous GWAS studies and listed in the GWAS Catalog using ANNOVAR software[187] (version 1 Feb 2016, accessed April 9, 2016).

9.2. Gene-based GWAS analysis

We performed gene-based testing with the full GWAS set (~2.5M HapMap-imputed SNPs) of both phenotypes using VEGAS.[192,193] This software has the advantage of accounting for LD structure and the possibility to define a range beyond the gene bounds to include intergenic regions in the analysis. We defined a 50kb extra window surrounding the genes and considered every SNP for the gene-based analysis, ran the analyses per chromosome with up to 10^6 permutations and considered $P<2.5x10^{-06}$ as the threshold for significance (0.05/~20.000 genes).

9.3. eQTL and mQTL analyses

eQTL[194] and mQTL[195] analyses performed by the BIOS consortium have been described previously. The methods described in these papers are summarized below.

Genotype data

The BIOS consortium used samples from five Dutch cohorts; genotype QC and generation was described previously for each cohort: The Leiden Longevity Study,[196] The Rotterdam Study,[197] The LifeLines-DEEP cohort,[198] The Cohort on Diabetes and Atherosclerosis Maastricht (CODAM)[199] and The Netherlands Twin Register.[200] Genotype data were harmonized towards the Genome of the Netherlands (Genome of the Netherlands Consortium, 2014) (GoNL) using Genotype Hamonizer and subsequently imputed per cohort using Impute2 using the GoNL reference panel (v5). We removed SNPs with an imputation info-score below 0.5, a HWE *P*-value smaller than 10^{-4}, a call rate below 95% or a minor allele frequency smaller than 0.05.

9.3.2 RNA data preparation, sequencing and quantification

Total RNA from whole blood was deprived of globin using Ambions GLOBINclear kit and subsequently processed for sequencing using Illumina's Truseq version 2 library preparation kit. Paired-end sequencing of 2x50bp was performed using Illumina's Hiseq2000, pooling samples at 10 per lane, and aiming for >15M read pairs per sample. Finally, read sets per sample were generated using CASAVA, retaining only reads passing Illumina's Chastity Filter for further processing. The quality of the raw reads was checked using FastQC. The adaptors identified by FastQC (v0.10.1) were clipped using cutadapt (v1.1) applying default settings (min overlap 3, min length). Sickle (v1.200) was used to trim low quality ends of the

reads (min length 25, min quality 20). Read alignment was performed using STAR 2.3.0e. To avoid reference mapping bias all GoNL SNPs with MAF > 0.01 in the reference genome were masked. Read pairs with at most 8 mismatches, mapping to at most 5 positions were used. Mapping statistics from the BAM files were acquired through Samtools flagstat (v0.1.19-44428cd). The 5' and 3' coverage bias, duplication rate and insert sizes were assessed using Picard tools (v1.86). We estimated expression on the gene, exon, exon ratio and polyA ratio levels using Ensembl v.71 annotation (which corresponds to Gencode v.16). Overlapping exons (on either of the two strands) were merged into meta-exons and expression was quantified for the whole meta-exon. To this end, custom scripts were developed which uses coverage per base from coverageBed and intersectBed from the Bedtools suite (v2.17.0) and R (v2.15.1). This resulted in base counts per exon or meta-exon. Expression data was first normalized using Trimmed Mean of M-values (TMM). Then expression values were log2 transformed, probe and sample means were centered to zero. To correct for batch effects, principal component analysis (PCA) was run on the sample correlation matrix and the first 25 PCs were removed. We saw that removing these PCs resulted in highest number of eQTLs detected. To ascertain that none of these 25 PCs are under genetic control, we ran separate QTL mapping on each principal component and ensured that there were no SNPs associated with them. After QC[194] data was available from 2,116 samples.

9.3.3 Methylation data generation, mapping and normalization.

For the generation of genome-wide DNA methylation data, 500 ng of genomic DNA was bisulfite modified using the EZ DNA Methylation kit (Zymo Research, Irvine, California, USA) and hybridized on Illumina 450k arrays according to the manufacturer's protocols. The original IDAT files were extracted from the HiScanSQ scanner. We remapped the 450K probes to the human genome reference (HG19) to correct for inaccurate mappings of probes and identify probes that mapped to multiple locations on the genome. Next, we removed probes with a known SNP (GoNL, MAF > 0.01) at the single base extension (SBE) site or CpG site. Lastly, we removed all probes on the sex chromosomes, leaving 405.709 high quality methylation probes for the analyses. Methylation data was directly processed from IDAT files resulting from the Illumina 450k array analysis. After QC,[195], data was available from 3,841 samples.

9.3.4 eQTL and mQTL analysis

For each of the 12 SNPs identified in the GWAS, local (cis, exons/methylation sites < 1 MB from the SNP) and genome-wide (trans, exons/methylation sites > 5 MB from the SNP) effects were identified by computing Spearman rank correlations between SNPs and local or global exons/methylation sites. Bonferroni multiple testing correction was performed for the 12 SNPs tested ($P<2.5x10^{-06}$ for cis mQTL analysis, $P<1x10^{-08}$ for trans mQTL analysis, $P<1.2\ x10^{-06}$ for cis eQTL analysis, $P<1.3x10^{-08}$ for trans eQTL analysis). For each of the significant associations, the exons/methylation sites were selected, the strongest eQTLs were identified for these exons/methylation sites, and LD between these strongest eQTLs and the corresponding SNP identified in the GWAS were computed. LD was computed using BIOS genotypes (the genotypes used for eQTL and mQTL mapping).

9.4. Functional variant analysis using RegulomeDB

We used RegulomeDB[201] to identify variants amongst the 322 SNPs that reached $P<5x10^{-08}$ for association with AFB and/or NEB in the meta-analysis of GWAS that likely influence regulation of gene expression. RegulomeDB integrates results from RoadMap Epigenomics[202] and the ENCODE project.[203] SNPs that showed most evidence of being functional – defined as a RegulomeDB score <4 – were subsequently examined in more detail in terms of effects on gene expression (eQTLs) and their protein-binding capacity (Supplementary Supplementary Table 6).

9.4.1 Gene prioritization using four bioinformatics approaches

Potentially causal genes for the associations identified by GWAS were identified using four previously described bioinformatics tools: ToppGene,[204] Endeavour,[205] MetaRanker,[206] and DEPICT.[207] To this end, we first retrieved positional coordinates for all lead SNPs according to GRCh37/hg19 using Ensembl's BioMart. These coordinates were used to subsequently extract all genes located within ±40kb of lead SNPs using the UCSC Supplementary Notebrowser. The identified genes then served as input for ToppGene and Endeavour. Genes with established roles in fertility served as training genes in this procedure, i.e. *BRCA1*, *EGFR*, *ERBB2-4*, *HSD17B1*, *RBM5*, *ESR1*, *ESR2* and *FSHB*. All 10 genes were used in the

pooled and sex-specific analyses, while *ESR1*, *ESR2* and *FSHB* were not used in the analyses in data from men only, for biological reasons. For MetaRanker we provided SNPs that reached $P<5x10^{-04}$ and their chromosomal position as input, together with the previously mentioned set of training genes. Since ToppGene, Endeavour and MetaRanker are biased towards larger and well-described genes, we additionally performed a gene prioritization procedure using DEPICT.[207] All SNPs that reached $P<5x10^{-04}$ in the meta-analysis served as input, and information on prioritized genes, gene set enrichment, and tissue/cell type enrichment were extracted. Genes were subsequently prioritized that reached: 1) $P<0.05$ in DEPICT; or 2) $P<0.05$ in ToppGene, Endeavour and MetaRanker (Supplementary Tables 11, 12).

9.5. Functional network and enrichment analyses

DEPICT was additionally used to identify gene set, cell type and tissue enrichment analyses, using the GWAS-identified SNPs with $P<5x10^{-04}$ as input.[c] Due to the relatively small number of identified loci, DEPICT was only able to perform these analyses for AFB and NEB pooled, and AFB women.

To construct a functional association network, we combined five prioritized candidate gene sets into a single query gene set: closest genes to the lead SNPs, closest genes to the nonsynonymous SNPs in high LD ($r^2>0.50$) with the corresponding lead SNP, closest genes to other types of SNPs in very high LD ($r^2>0.80$) with the corresponding lead SNP, and expression probe gene names of cis, and trans eQTLs. The single query gene set was then used as input for the functional network analysis.[183] We applied the GeneMANIA algorithm together with its large set of accompanying functional association data.[208] We used the Cytoscape software platform,[209] extended by the GeneMANIA plugin (Data Version:

[c] We initially used a threshold of P<1E-5 for association with the respective outcomes in the meta-analyses of GWAS for SNPs to serve as input for the gene and tissue set enrichment analyses, as per the developers' recommendations.[206] We contacted the 1st author when this did not yield gene and tissue sets that were significantly enriched, and were advised to apply the slightly more lenient inclusion criterion of P<5E-4.

8/12/2014, accessed April 24, 2016).[210] All the genes in the composite network, either from the query or the resulting gene sets, were then used for functional enrichment analysis against Gene Ontology terms (GO terms)[211] to identify the most relevant GO terms using the same plugin.[210]

10. GENE-ENVIRONMENT INTERACTIONS

Previous research based on twin studies shows differential heritability of fertility behavior across birth cohorts.[212,213] With the exception of one recent mega-analysis[112] and a recent related study,[214] we are not aware of any study that examines variation at the molecular level to understand whether the genetic effect of AFB and NEB changes across birth cohort, level of education or other environmental factors. There is an implicit assumption that the genes associated with phenotypes are often constant across different historical, geographic or socio-economic groups.[39] In this section, we therefore examine gene-environment interaction by birth cohort and educational attainment.

As elaborated upon already in detail in Section 1.5, there has been considerable environmental variation over time and among cohorts in different historical periods that has undoubtedly influenced AFB and NEB. It is plausible, therefore, that there are differences across birth cohorts (time) since individuals born in different periods face diverse environmental conditions, such as the introduction and availability of effective contraception, sexual norms and diversity in factors that 'compete' with fertility, such as the expansion of educational attainment and labor force participation of women.[7]

This builds upon research that has examined changes across cohorts on the genetics of smoking. An early study adopted a twin design to demonstrate that genetic factors underlying smoking desistance were more important after the introduction of a restrictive legislation on smoking.[215] A related study also showed strong genetic influences on smoking of cohorts born in the 1920s, 1930s and 1950s, but not for those born in the 1940s and 1960s. They link these differences to changes in legislation prohibiting smoking in public places.[216] Using GREML methods and a modified DeFries-Fulker approach, a recent study likewise

demonstrated that there were cohort differences in the genetic influence on smoking, which increased over time.[113]

It may also be the case that the PGS for AFB and NEB is moderated by educational attainment. If the genetic association operates differently by the level of educational attainment, it would provide additional insight into understanding how fertility preferences and education are transmitted across generations. A recent study using the HRS in the US suggested that natural selection has taken place in contemporary societies and that there has been slow selection of lower educational attainment for both sexes.[214] In other words, the study argues that individuals endowed with genes predisposing them to more years of education are having fewer children and that natural selection (of those born from the 1930s to 1953) favors variants associated with less education. A commentary on this article[39] emphasizes four main reasons to be tentative about the conclusions that can be drawn. First, selection on education is weak and evolutionary changes are slow. Second, the PGS for educational attainment is likely associated with many other (non)cognitive traits. Third, socio-environmental, cultural and economic factors often override genetic factors for this phenotype. Fourth, 'years of education' is not a precise measurement and finally, that there may be mortality selection in the HRS sample of genotyped individuals, who have a higher socioeconomic status.[217]

10.1 Cohort analysis

We used the Swedish Twin Register (STR) to examine if the effect of a polygenic score (PGS) of AFB and NEB varies across birth cohort. We followed the analysis presented in the recent GWAS of education[218] and divide the sample into six groups based on their year of birth. Each group spans five birth years, with the oldest ranging from 1929-1933 and the youngest born between 1954- 1958. We then estimated the following regressions:

$$AFB_i = \beta_0 + \beta_1 PGS^{AFB}{}_i + \beta_2 Sex_i + \sum_{c=1}^{6} \gamma_1^c cohort_{ci} + \sum_{c=1}^{6} \gamma_2^c PGS^{AFB}{}_i \times cohort_{ci} + \sum_{k=1}^{10} \beta_k^{pc} PC^k{}_i + \varepsilon_i$$

$$NEB_i = \beta_0 + \beta_1 PGS^{NEB}{}_i + \beta_2 Sex_i + \sum_{c=1}^{6} \gamma_1^c cohort_{ci} + \sum_{c=1}^{6} \gamma_2^c PGS^{NEB}{}_i \times cohort_{ci} + \sum_{k=1}^{10} \beta_k^{pc} PC^k{}_i + \varepsilon_i$$

where i indicate individuals and k indexes principal components ( ) of the genetic data. We used a PGS standardized to have mean 0 and standard deviation 1 based on the GWAS meta-analysis results excluding the STR (details on how we constructed the PGS are available in Section 7 of the SI). The coefficients γ_2^c estimate whether there is an interaction between the PGS and an individual's birth cohort.

Supplementary Table 38 reports the estimated coefficient from these regressions. The results indicate a U-shaped trend in AFB and a linear decline in NEB, but do not provide any clear evidence of interaction effects between the PGS's and birth cohort. The only interaction coefficient that is significantly different from zero is the interaction between the PGS for NEB in the most recent birth cohort (those born 1954-1958). This analysis is a first descriptive attempt to examine GxE effects with birth cohorts. However, the PGSs are weighted by association coefficients of a GWAS where each cohort consists of individuals born in different years. Moreover, individual cohorts controlled for linear, quadratic and cubic trends in fertility behavior in their analysis. It would be informative to extend these analyses to more recent cohorts and contexts and refine the approach.

10.2 Educational attainment

We tested the interaction effects between educational level and the PGS of AFB and NEB in three different samples (LifeLines, STR and HRS). To ensure out of sample prediction, the PGS excluded each respective sample as required.

For each cohort, we estimated the following regressions[d]:

$$AFB_i = \beta_0 + \beta_1 PGS^{AFB}{}_i + \beta_2 Sex_i + \beta_3 education_i + \beta_4 PGS^{AFB}{}_i \times education_i + \sum_{k=1}^{10} \beta_k^{pc} PC^k{}_i + \varepsilon_i$$

$$NEB_i = \beta_0 + \beta_1 PGS^{NEB}{}_i + \beta_2 Sex_i + \beta_3 education_i + \beta_4 PGS^{NEB}{}_i \times education_i + \sum_{k=1}^{10} \beta_k^{pc} PC^k{}_i + \varepsilon_i$$

[d] For HRS, we estimated only a PGS for NEB, since AFB is not collected in that data.

Where $education_i$ is measured as years of education. Supplementary Table 39 reports the estimated coefficient from these regressions. The results indicate that years of education are positively associated with AFB in both LifeLines and STR, and negatively associated with NEB in the HRS. With the exception of NEB in the HRS, we found no evidence of GxE effects with education. We can therefore conclude that it appears that education does not appear to moderate the effect of the PGS for AFB and NEB.

11. ROBUSTNESS CHECKS

To estimate the robustness of our results for AFB, we conducted two additional analyses. First, we estimated how the coefficients change if we control for Educational Attainment (EA). Using data from deCODE, we ran an additional association analysis using the 10 loci that were genome-wide significant in the meta-analysis (p-value<$5x10^{-08}$). The analysis has been restricted to individuals born between 1910 and 1975, who also had data available on completed education. The total sample size is 42,187 (17,996 males and 24,191 females). The analysis is adjusted for sex, year of birth (linear, squared and cubic), interaction between sex and year of birth and the first 10 PCAs. Education is measured by years of education, ranging between 10 and 20 years. Supplementary Table 40 reports the association results before and after adjusting for educational attainment. Our analysis shows that the effect sizes shrink after including educational attainment as a covariate, with an average reduction of around 15%. We also estimated the effect of a polygenic risk score of AFB calculated from meta-analysis data excluding the deCODE cohort. The polygenic score remains highly significant. The effect of 1SD of the AFB score decreases from 0.19 years (69 days) without controlling for education to 0.16 years (59 days) when we control for years of education. To summarize, this analysis shows that the coefficients are robust to the inclusion of educational attainment in the model.

Second, we estimated how the coefficients change after controlling for Education Attainment (EA) and Age at First Sex using the UKBiobank (N=50,954). We ran two association models: the first follows the GWAS analysis plan with no additional covariates and the second added years of education and age at first sexual intercourse as covariates. The results are presented in Supplementary Table 41 and Supplementary Figure 37. Our analysis shows

that the effect sizes of our top hits are highly concordant (R^2=0.94). The inclusion of EA and AFS as covariates weakens the effect sizes on average by 40% and increases the p-value of the estimated coefficients. However, both EA and AFS have a significant genetic basis and are highly genetically correlated with AFB. Therefore, possible genetic pleiotropy may affect the results and capture a considerable proportion of the genetic effect. Nevertheless, 7 SNPs out of 10 tested, have a p-value<0.05 in the model that controls for EA and AFS. Overall, we interpret this additional analysis as a robustness test that confirm that the top hits from our meta-analysis are robust to the inclusion of the confounding factors of EA and AFS

12. POSITIVE SELECTION

We performed a Haploplotter analysis[219] to examine if lead SNPs and/or functional variants identified using RegulomeDB show evidence of positive selection. Three variants showed standardized integrated haplotype scores <-2 or >2, indicating that these variants represent the top 5% of signals in the population. These SNPs are: 1) rs7628058 on chromosome 3 for AFB, an eQTLs for *RBM6* in monocytes; 2) rs2247510 on chromosome 3 for AFB, an eQTL for *RBM6* and *HYAL3* in monocytes and binding site for a range of transcription factors; 3) rs2415984, the lead SNP in the chromosome 14 locus for NEB. Results are presented in Supplementary Table 42.

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External scientists can apply to the Steering Committee of BASE-II for data access. Although the data are available for other parties are scientific data and not personal contact data, the scientific data are subject to a security level as if they were personal data to ensure that the BASE-II Steering Committee sufficiently protects the large volume of data collected from each BASE-II participant. All existing variables are documented in a handbook. Contact: Katrin Schaar, scientific coordinator, schaar@mpib-berlin.mpg.de.

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CROATIA cohorts

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deCODE

All deCODE collaborators in this study are employees of deCODE Genetics/Amgen, Inc. External researchers who wish to obtain access to data or EA2 results may contact Gudmar Thorleifsson gudmar.thorleifsson@decode.is.

DESIR

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EPIC-Norfolk

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Dortmund Health Study DHS

DHS (Dortmund Health Study) - The collection of sociodemographic and clinical data in the Dortmund Health Study was supported by the German Migraine & Headache Society (DMKG) and by unrestricted grants of equal share from Almirall, Astra Zeneca, Berlin Chemie, Boehringer, Boots Health Care, Glaxo-Smith-Kline, Janssen Cilag, McNeil Pharma, MSD Sharp & Dohme and Pfizer to the University of Muenster. Blood collection in the Dortmund Health Study was done through funds from the Institute of Epidemiology and Social Medicine University of Muenster. Genotyping for the Human Omni Chip was supported by the German Ministry of Education and Research (BMBF, grant no. 01ER0816). Researchers interested in using DHS data are required to sign and follow the terms of a Cooperation Agreement that includes a number of clauses designed to ensure protection of

privacy and compliance with relevant laws. For further information, contact Klaus Berger (bergerk@uni-muenster.de).

Finnish Twin Cohort

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Generation R

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The study protocol was approved by the Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam. Written informed consent was obtained from all participants. The general design of Generation R Study is made possible by financial support from the Erasmus Medical Center, Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organisation for Scientific Research (NWO), the Ministry of Health, Welfare and Sport and the Ministry of Youth and Families. Vincent W. Jaddoe received an additional grant from the Netherlands Organization

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GENOA

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GOYA

The Danish National Research Foundation established the Danish Epidemiology Science Centre, which initiated and created the Danish National Birth Cohort. The cohort is a result of a major grant from this Foundation. Additional support for the Danish National Birth Cohort was obtained from the Pharmacy Foundation, the Egmont Foundation, the March of Dimes Birth Defects Foundation, and the Augustinus Foundation. Genotyping for the GOYA Study within the Danish National Birth Cohort was funded by the Wellcome Trust (Grant ref: 084762MA).

HBCS

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Health 2000

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Health ABC

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HRS

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HRS (Health and Retirement Study): Genotype data can be accessed via the database of Genotypes and Phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/gap, accession number phs000428.v1.p1). Researchers who wish to link genetic data with other HRS measures that are not in dbGaP, such as fertility data, must apply for access from HRS. See the HRS website (http://hrsonline.isr.umich.edu/gwas) for details.

HTO

We thank all the families who contributed to this study. Phenotyping and genotyping of the HTO cohort was funded by the Wellcome Trust, the UK Medical Research Council and the British Heart Foundation. Data are available upon request from the Principal Investigator, Bernard Keavney (bernard.keavney@manchester.ac.uk).

INGI-CARL

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INGI-Val Borbera

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LBC1921 and LBC1936
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LIFELINES
Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviors of 167,729 persons

living in the North of The Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics.[220,221]

The Lifelines Cohort Study, and generation and management of GWAS genotype data for the Lifelines Cohort Study is supported by the Netherlands Organization of Scientific Research NWO (grant 175.010.2007.006), the Ministry of Economic Affairs, the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the Northern Netherlands Collaboration of Provinces (SNN), the Province of Groningen, University Medical Center Groningen, the University of Groningen, Dutch Kidney Foundation and Dutch Diabetes Research Foundation. The authors wish to acknowledge the services of the Lifelines Cohort Study, the contributing research centers delivering data to Lifelines, and all the study participant. Data availability: Lifelines is a facility that is open for all researchers. Information on application and data access procedure is summarized on www.lifelines.net.

Longevity

National Institutes of Health (AG028872, CA164468 and DA033788 to A.B., AG042188 to G.A., AG021654-01 and AG-18728-02A1 to N.B.) and the Glenn Center for the Biology of Human Aging.

MCTFR

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MoBa

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MrOS Sweden

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Data availability

Data are available upon request from the NESDA data management bureau.

Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS)

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NTR (Netherlands Twin Register)

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OGP Ogliastra Genetic Park

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Rotterdam Study

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Sorbs

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THISEAS

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from the Netherlands Organization for Scientific Research (NWO Veni grant 016.165.004). Researchers using the data are required to follow the terms of an Assistance Agreement containing a number of clauses designed to ensure protection of privacy and compliance with relevant laws. For Further information, contact Patrik Magnusson (Patrik.magnusson@ki.se).

TwinsUK

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UKBiobank

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