Supplementary Text

Ethical approvals

The deCODE study was approved by the Icelandic National Bioethics Committee (VSN-15-169). The North West Research Ethics Committee reviewed and approved UK Biobank's scientific protocol and operational procedures (REC reference no.: 06/MRE08/65).

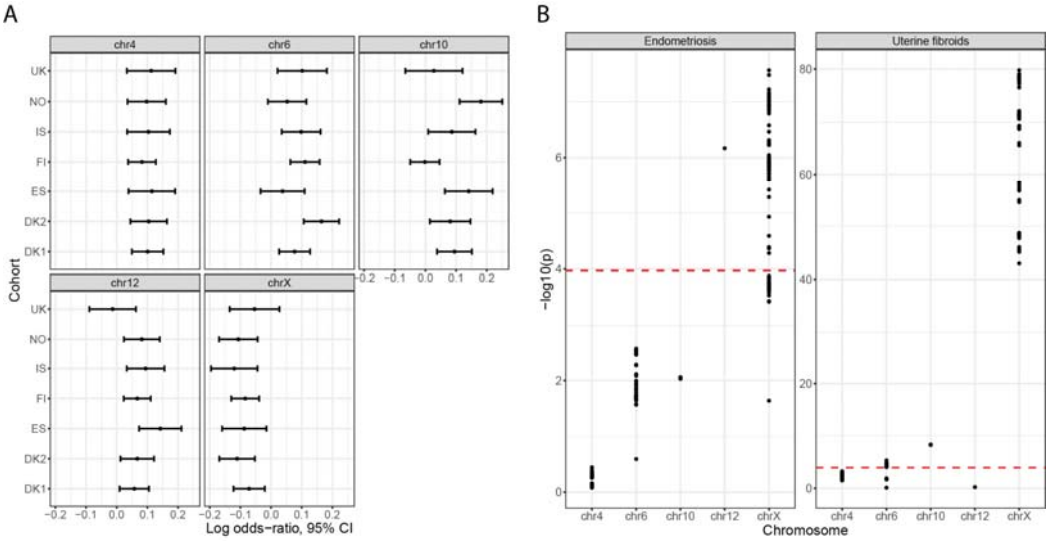
Approval of the Copenhagen Hospital Biobank Reproductive Health Study (CHB-RHS) was obtained from the Danish National Committee on Health Research Ethics (NVK-1805807) and the Capital Region Data Protection Agency (P-2019-49).

All study participants provided a signed informed consent, and the study protocol has been approved by the administrative board of the Norwegian Mother, Father and Child Cohort Study, led by the Norwegian Institute of Public Health. The establishment of MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from The Regional Committee for Medical Research Ethics. The study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics South-East (2015/2425) and by the Swedish Ethical Review Authority (Dnr 2022-03248-01).

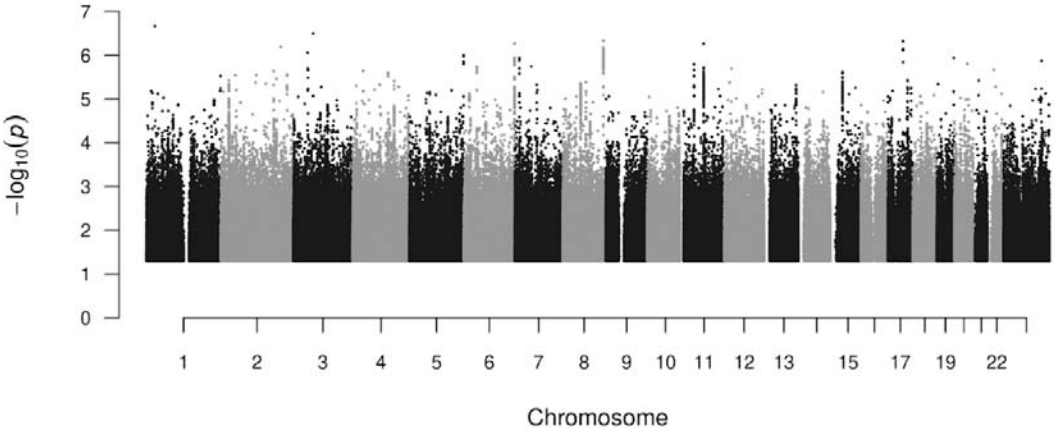
Participants in FinnGen provided informed consent for biobank research on basis of the Finnish Biobank Act. Alternatively, separate research cohorts, collected before the Finnish Biobank Act came into effect (in September 2013) and the start of FinnGen (August 2017) were collected on the basis of study-specific consent and later transferred to the Finnish biobanks after approval by Fimea, the National Supervisory Authority for Welfare and Health. Recruitment protocols followed the biobank protocols approved by Fimea. The Coordinating Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS) approved the FinnGen study protocol (number HUS/990/2017). The FinnGen study is approved by the Finnish Institute for Health and welfare (approval number THL/2031/6.02.00/2017, amendments THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019 and THL/1721/5.05.00/2019), the Digital and Population Data Service Agency (VRK43431/2017-3, VRK/6909/2018-3 and VRK/4415/2019-3), the Social Insurance Institution (KELA) (KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019 and KELA 98/522/2019) and Statistics Finland (TK-53-1041-17).

The activities of the EstBB are regulated by the Human Genes Research Act, which was adopted in 2000 specifically for the operations of the EstBB. All Estonian Biobank participants have signed a broad informed consent form and analyses were carried out under ethical approval 1.1-12/624 from the Estonian Committee on Bioethics and Human Research (Estonian Ministry of Social Affairs) and data release N05 from the EstBB.

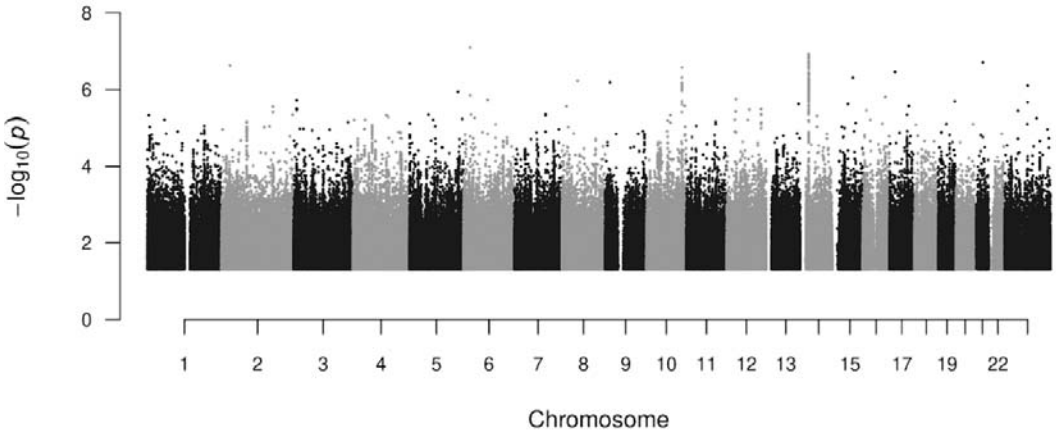
Supplementary Figures



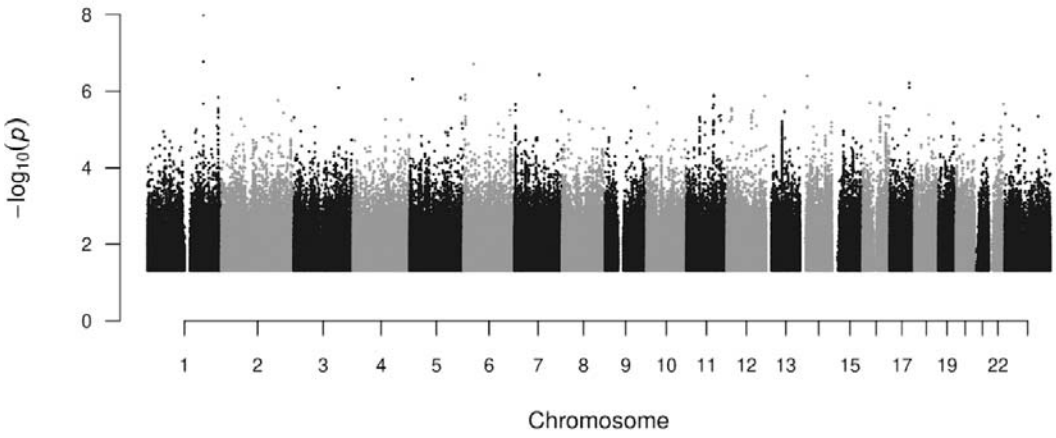
*Supplementary Figure 1. (A) Effect sizes in each cohort for the postpartum hemorrhage lead variants, which were largely similar. (B) Genome-wide significant variants from the postpartum hemorrhage analysis are also associated with endometriosis and uterine fibroids. The red line indicates the Bonferroni corrected p-value threshold (p < 0.05/(2 loci * 234 variants) = 0.0001).*



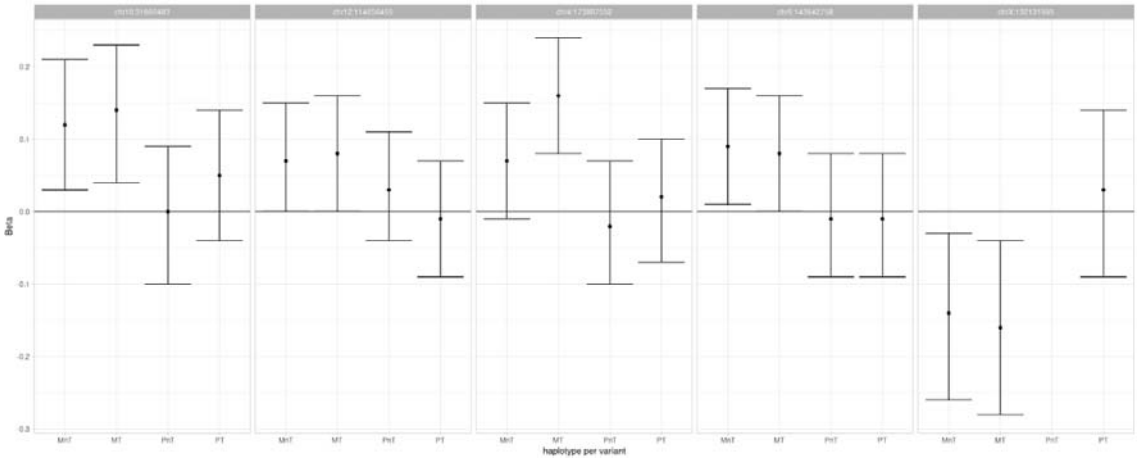
Supplementary Figure 2. Manhattan plot for Early bleeding, all outcomes.



Supplementary Figure 3. Supplementary Figure 2: Manhattan plot for Early bleeding, ending in live birth.



Supplementary Figure 4. Manhattan plot for antepartum hemorrhage



Supplementary Figure 5. Haplotype analysis of the five PPH associated variants in the MoBa and deCODE cohorts. Results suggest that that effect is mediated through the maternal genome. Mnt: maternal non-transmitted; MT: maternal transmitted; PnT: paternal non-transmitted; PT: paternal transmitted

Supplementary Tables

Supplementary Table 1. The contribution from each of the six Northern European cohorts. n.a. indicates the phenotype was not available in the cohort.

PHENOTYPE	CHB/DBDS		EGCUT		DECODE		FINNGEN R6		MOBA		UK BIOBANK		TOTAL	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Early bleeding versus all pregnancies	10.648	70.923	10.013	23.475	388	55.588	6.380	140.681	n.a.	n.a.	1.469	12.227	28.898	302.894
Early bleeding in women giving birth	5.474	50.733	n.a.	n.a.	380	55.462	n.a.	n.a.	n.a.	n.a.	502	12.227	6.356	118.422
Antepartum hemorrhage	1.726	54.227	199	24.783	672	55.079	n.a.	n.a.	n.a.	n.a.	639	12.361	3.236	146.450
Postpartum hemorrhage	7.435	43.916	1.846	22.057	2.897	52.730	4.783	108.033	2.972	21.337	1.579	11.427	21.512	259.500
PPH – Atonic	4.597	43.916	995	22.713	1.895	53.623	1.600	108.033	2.739	21.549	1.222	11.975	13.048	261.809
PPH – Retained placenta	2.500	43.916	393	23.218	705	54.815	2.142	108.033	299	23.989	217	12.456	6.256	266.427

Supplementary Table 2. Effect sizes (95% CI and P-value) for the lead variants of PPH for the atoni and retained placenta subtypes, respectively.

CHR	RSID	ATONI	RETAINED PLACENTA	CASE-CASE GWAS
4	rs13141656	1.10 (1.08-1.13; 9.6e-16)	1.12 (1.06-1.19; 0.00019)	1.04 (0.99-1.09; 0.09)
6	rs12195857	1.10 (1.08-1.12; 2e-14)	1.12 (1.06-1.17; 4.8e-05)	1.03 (0.98-1.08; 0.26)
10	rs11591307	1.08 (1.05-1.10; 1.4e-09)	1.10 (1.02-1.18; 0.019)	1.05 (0.99-1.10; 0.08)
12	rs11067228	1.07 (1.05-1.10; 5e-09)	1.08 (1.04-1.13; 0.00053)	1.01 (0.97-1.06; 0.56)
X	rs2747025	0.91 (0.88-0.95; 3.1e-08)	0.92 (0.90-0.95; 2.1e-10)	1.05 (0.99-1.10; 0.05)

Supplementary Table 3. LDSC statistics and inflation metrics

PHENOTYPE	LDSC H2, OBSERVED SCALE (SE)	LDSC INTERCEPT	RATIO	MEAN CHI^2
Early bleeding in pregnancy, all outcomes	0.0144 (0.0017)	1.005	0.0688	1.08
Early bleeding in pregnancy, live birth as outcome	0.009 (0.0035)	0.9929	<0	1.02
Antepartum hemorrhage	0.0005 (0.0029)	0.9975	NA	1
Postpartum hemorrhage	0.0149 (0.002)	1.0175	0.176	1.10
Postpartum hemorrhage due to atony	0.0101 (0.0018)	1.0092	0.1437	1.06
Postpartum hemorrhage due to retained placenta	0.0088 (0.0018)	0.99	<0	1.05

Supplementary Table 4: Variants previously associated with traits in the GWAS catalog ($p < 5 \cdot 10^{-8}$), and variants in strong LD ($r^2 > 0.8$) with other variants.

CHROMOSOME	LEAD VARIANT	GWAS TRAIT, AS LISTED IN THE GWAS CATALOG	VARIANT IN LD	R^2
6	rs12195857	Educational attainment	rs12200809	0.83
10	rs11591307	Uterine fibroids	rs11008551	0.98
10	rs11591307	Uterine fibroids	rs10508765	0.96
10	rs11591307	Uterine leiomyomata	rs7090544	0.97
12	rs11067228	Heel bone mineral density	rs11067228	1
12	rs11067228	Prostate-specific antigen levels	rs11067228	1
12	rs11067228	Serum prostate-specific antigen levels	rs11067228	1
X	rs2747025	Endometriosis	rs5933091	1
X	rs2747025	Serum creatinine levels	rs5933079	1
X	rs2747025	Uterine fibroids	rs5930554	1
X	rs2747025	Uterine fibroids	rs12392108	1
X	rs2747025	Uterine leiomyomata	rs5930554	1

Supplementary Table 5. Post-partum hemorrhage (PPH) lead association sequence variants along with their correlated variants (r2>0.80) intersect with enhancer-like sequences (ELS) and CTCF binding sites as defined in ENCODE´s encyclopaedia of candidate cis-regulatory elements (cCRE).

CCRE TYPE	*CHR10:31660483:SG*	*CHR12:114656455:SG*	*CHR4:173807552:SG*	*CHR6:143642758:SG*	*CHRX:132131995:SG*
CTCF-only-CTCF-bound					chrX:132231235:SG
dELS	chr10:31623817:IG.0:0, chr10:31623817:IG.0:1, chr10:31623818:M:2, chr10:31666087:SG		chr4:173807415:SG, chr4:173807552:SG		chrX:132294819:SG, chrX:132353729:IG:0, chrX:132353729:IG:1
dELS-CTCF-bound	chr10:31660483:SG				chrX:132369722:SG
pELS-CTCF-bound		chr12:114656455:SG		chr6:143678453:IG	

Supplementary Table 6. Enriched cCRE by Samples: PPH signals were tested for enrichment within cCREs of 1519 different samples representing 421 different tissues or cell types (UBERON and CL IDs). Shown are nominally significant results (P<0.05).

TISSUE /CELL LINE	ENCODE IDS	ANNOTATED PPH SIGNALS, N	*P*-VALUE	EXPECTED PROPORTION OF ANNOTATED PPH SIGNALS	GENOME COVERED (BP) BY ANNOTATION
uterus	ENCFF434PEE	5/5	0.00709	39%	62148258
uterus	ENCFF938GZV	4/5	0.02003	27%	28616727
urinary bladder	ENCFF225SLW	4/5	0.02326	29%	32611476
forelimb muscle	ENCFF193CYW	4/5	0.02412	29%	32101010

Supplementary Table 7. GWA signals in cCREs: PPH signals were nominally enriched within cCREs found in four (out of 1519) samples representing three different tissues (uterus, urinary bladder and forelimb muscle). Shown are the lead sequence variants (columns) or their correlated variants that were found in overlap with cCREs as defined in each of the five samples.

TISSUE /CELL LINE	ENCODE IDS	*CHR10:31660483:SG*	*CHR12:114656455:SG*	*CHR4:173807552:SG*	*CHR6:143642758:SG*	*CHRX:132131995:SG*
uterus	**uterus (ENCFF434PEE)**	*chr10:31623817:IG.0:0, chr10:31623817:IG.0:1, chr10:31623818:M:2, chr10:31660483:SG*	*chr12:114656455:SG*	*chr4:173807415:SG, chr4:173807552:SG*	*chr6:143678453:IG*	chrX:132369722:SG
uterus	**uterus (ENCFF938GZV)**	chr10:31623817:IG.0:0, chr10:31623817:IG.0:1, chr10:31623818:M:2, chr10:31660483:SG	chr12:114656455:SG	chr4:173807415:SG, chr4:173807552:SG	chr6:143678453:IG	
urinary bladder	**urinary bladder (ENCFF225SLW)**	*chr10:31623817:IG.0:0, chr10:31623817:IG.0:1, chr10:31623818:M:2, chr10:31660483:SG*	*chr12:114656455:SG*	*chr4:173807415:SG, chr4:173807552:SG*	*chr6:143678453:IG*	
forelimb muscle	**forelimb muscle (ENCFF193CYW)**	*chr10:31623817:IG.0:0, chr10:31623817:IG.0:1, chr10:31623818:M:2*		*chr4:173807415:SG, chr4:173807552:SG*	*chr6:143678453:IG*	chrX:132369722:SG

Supplementary Table 8. Enriched epimap: PPH signals were tested for enrichment within enhancers (A/G) as defined in 833 samples by Epimap. Shown are nominally significant results (P<0.05).

TISSUE /CELL LINE	EPIMAP IDS	ANNOTATED PPH SIGNALS, N	*P*-VALUE	EXPECTED PROPORTION OF ANNOTATED PPH SIGNALS	GENOME COVERED (BP) BY ANNOTATION
UTERUS	BSS01884	4/5	0.0085	22%	50940614
MESENDODERM DERIV	BSS01263	3/5	0.013	12%	22150855

Supplementary Table 9. Predicted gene targets, Epimap: PPH signals were most strongly enriched among enhancers (Active/Genic) found in uterus and three other tissues in Epimap. Shown is the intersection for each PPH signal (lead variant and their correlated variants given r2>0.80) with enhancers in each of the most strongly enriched tissues where P<0.05, nominally significant, and the predicted gene target for those enhancers.*

TISSUE / CELL-TYPE	***10P11.22 (CHR10:31660483:SG)***	***12Q24.21 (CHR12:114656455:SG)***	***6Q24.2 (CHR6:143642758:SG)***	***XQ26.2 (CHRX:132131995:SG)***	***4Q34.1 (CHR4:173807552:SG)***
UTERUS		TBX3 (chr12:114656455:SG)		FRMD7 (chrX:132120786:SG,chrX:132126844:SG), RAP2C (chrX:132266705:SG)	
MESENDODERM_DERIV		TBX3 (chr12:114656455:SG)		FRMD7 (chrX:132120786:SG)	

Supplementary Table 10. Haplotype effect estimates for the five PPH associated loci.

		MOBA			DECODE			META				
	Haplotype Variant	effect	95%CI	P	effect	95%CI	P	effect	95%CI	P	P_het	I2
MT	chr10:31660483	0.13	(0.03;0.22)	0.0099	0.23	(-0.08;0.54)	0.15	0.14	(0.04;0.23)	0.0039	0.53	0
	12:114656455	0.07	(-0.01;0.15)	0.095	0.2	(-0.05;0.46)	0.11	0.08	(0.00;0.16)	0.038	0.32	0.9
	4:173807552	0.16	(0.08;0.25)	0.00019	0.13	(-0.16;0.42)	0.37	0.16	(0.08;0.24)	0.00012	0.83	0
	6:143642758	0.06	(-0.03;0.15)	0.17	0.24	(-0.02;0.50)	0.071	0.08	(-0.00;0.16)	0.060	0.20	38.9
	X:132131995	-0.16	(-0.28.-0.04)	0.0099	-0.13	(-0.56;0.31)	0.57	-0.16	(-0.28.-0.04)	0.0084	0.88	0
MnT	10:31660483	0.12	(0.03;0.22)	0.012	0.09	(-0.26;0.44)	0.60	0.12	(0.03;0.21)	0.010	0.88	0
	12:114656455	0.06	(-0.02;0.14)	0.17	0.25	(-0.02;0.52)	0.066	0.07	(-0.00;0.15)	0.065	0.17	45.9
	4:173807552	0.06	(-0.02;0.15)	0.15	0.12	(-0.18;0.43)	0.43	0.07	(-0.01;0.15)	0.11	0.72	0
	6:143642758	0.07	(-0.01;0.16)	0.095	0.28	(0.00;0.55)	0.046	0.09	(0.01;0.17)	0.028	0.16	49
	X:132131995	-0.17	(-0.30.-0.05)	0.0048	0.06	(-0.25;0.36)	0.71	-0.14	(-0.26.-0.03)	0.013	0.17	48
PT	10:31660483	0.04	(-0.06;0.13)	0.47	0.18	(-0.13;0.50)	0.25	0.05	(-0.04;0.14)	0.3	0.38	0
	12:114656455	-0.03	(-0.11;0.05)	0.48	0.17	(-0.08;0.43)	0.18	-0.01	(-0.09;0.07)	0.80	0.13	55.4
	4:173807552	0.02	(-0.06;0.11)	0.62	-0.07	(-0.36;0.23)	0.66	0.02	(-0.07;0.10)	0.72	0.58	0
	6:143642758	-0.04	(-0.13;0.05)	0.38	0.28	(0.02;0.54)	0.035	-0.01	(-0.09;0.08)	0.88	0.023	80.8
	X:132131995	0.02	(-0.09;0.14)	0.69	0.04	(-0.38;0.46)	0.85	0.03	(-0.09;0.14)	0.66	0.94	0
PnT	10:31660483	-0.01	(-0.11;0.09)	0.80	0.11	(-0.25;0.47)	0.55	0	(-0.10;0.09)	0.93	0.52	0
	12:114656455	0.04	(-0.04;0.12)	0.37	-0.02	(-0.32;0.27)	0.89	0.03	(-0.04;0.11)	0.41	0.71	0
	4:173807552	-0.01	(-0.10;0.08)	0.83	-0.13	(-0.48;0.21)	0.44	-0.02	(-0.10;0.07)	0.69	0.49	0
	6:143642758	0	(-0.09;0.08)	0.94	-0.04	(-0.34;0.27)	0.82	-0.01	(-0.09;0.08)	0.90	0.84	0
	12:114656455	0.04	(-0.04;0.12)	0.37	-0.02	(-0.32;0.27)	0.89	0.03	(-0.04;0.11)	0.41	0.71	0
	4:173807552	-0.01	(-0.10;0.08)	0.83	-0.13	(-0.48;0.21)	0.44	-0.02	(-0.10;0.07)	0.69	0.49	0
	6:143642758	0	(-0.09;0.08)	0.94	-0.04	(-0.34;0.27)	0.82	-0.01	(-0.09;0.08)	0.90	0.84	0

Mnt: maternal non-transmitted; MT: maternal transmitted; PnT: paternal non-transmitted; PT: paternal transmitted

Supplementary Table 11. Data sets used to generate summary statistics for genetic correlation analysis. ICE: deCODE genetics; GBR: UK Biobank; DNK: CHB/DBDS; FIN: FinnGen r7

Trait	*PPH*	*EB*	*Analysis*	*cases*	*ctrls*	*Datasets/Reference*
Pregnancy loss		*x*	*meta*	*49.996*	*174.109*	*PMID: 33239672*
Uterine fibroids	*x*	*x*	*meta*	*49.418*	*893.310*	*ICE_GBR_FIN*
Endometriosis	*x*	*x*	*meta*	*25.137*	*881.619*	*ICE_GBR_DNK_FIN*
Gestational diabetes	*x*		*meta*	*9.507*	*928.959*	*ICE_GBR_FIN*
Birth weight, fetal	*x*		*meta*	*419.140*		*PMID: 34282336*
Birth weight, maternal	*x*		*meta*	*268.129*		*PMID: 34282336*
Gestational age, maternal	*x*		*GWAS*	*59.496*		*ICE*
Gestational age, fetal	*x*		*GWAS*	*125.228*		*ICE*
Body mass index	*x*	*x*	*meta*	*509.458*		*ICE_GBR*
Smoking			*meta*	*313.810*	*581.902*	*ICE_GBR_FIN*
Alcohol dependence			*meta*	*29.557*	*707.411*	*ICE_GBR*
Education years			*GWAS*	*403.567*		*GBR*
Risk taking			*GWAS*	*107.158*	*323.889*	*GBR*
HDL Cholesterol			*meta*	*548.375*		*ICE_GBR*
Type 2 diabetes	*x*	*x*	*meta*	*88.062*	*916.726*	*ICE_GBR_FIN*
Systolic blood pressure	*x*	*x*	*meta*	*508.767*		*ICE_GBR*
Diastolic blood pressure	*x*	*x*	*meta*	*508.764*		*ICE_GBR*
Hypertension	*x*	*x*	*meta*	*347.202*	*901.986*	*ICE_GBR_DNK_FIN*
Coronary artery disease	*x*	*x*	*meta*	*172.831*	*1.051.258*	*ICE_GBR_DNK_FIN*
Myocardial infarction	*x*	*x*	*meta*	*76.141*	*1.121.254*	*ICE_GBR_DNK_FIN*
Atrial fibrilation	*x*	*x*	*meta*	*108.925*	*970.342*	*ICE_GBR_DNK_FIN*
Heart failure	*x*	*x*	*meta*	*88.888*	*1.184.381*	*ICE_GBR_DNK_FIN*
Stroke ischemic		*x*	*meta*	*83.860*	*1.049.069*	*ICE_GBR_FIN PMID: 29531354*

Stroke intracerebral hemorrhage		*x*	*daisy*	*12.224*	*339.944*	*ICE*
Post traumatic stress disorder	*x*	*x*	*meta*	*5.067*	*1.023.714*	*ICE_GBR_USA_FIN*
Stress	*x*	*x*	*GWAS*	*12.655*	*19.225*	*PMID: 31116379*
Major depression	*x*	*x*	*meta*	*59.851*	*113.154*	*PMID: 29700475*
Asthma	*x*	*x*	*meta*	*125.769*	*842.132*	*ICE_GBR_FIN*
Hypothyroidism	*x*	*x*	*meta*	*62.503*	*787.353*	*ICE_GBR_FIN*
Cholelithiasis	*x*	*x*	*meta*	*23.087*	*721.958*	*ICE_GBR*

Supplementary Table 12: Effect sizes for the standardized polygenic risk scores of PPH and birth weight.

VARIABLE	EFFECT SIZE, LOG-ODDS	95% CI
PPH	1.08	1.05;1.11
Birth weight	1.14	1.10; 1.17

Supplementary Table 13: Cohort definitions

PHENOTYPE	CODES	EXCLUSION	NOTE
Bleeding in early pregnancy ending in any outcome	ICD8: ICD9: ICD10:O20.*	Known coagulation disorders (D66-D69, O46.0, O67.0)	
Bleeding in early pregnancy leading to live birth	ICD8: ICD9: ICD10:O20.*	Known coagulation disorders (D66-D69, O46.0, O67.0)	Code must have occurred within the gestational period leading to a stillbirth or livebirth.
Antepartum hemorrhage	ICD8: ICD9: ICD10: O46	Known coagulation disorders (D66-D69, O46.0, O67.0)	
Postpartum hemorrhage	ICD8: ICD9: ICD10: O72 Post-2012 (DK only): ICD10: O72 (with >500mL blood loss)	Known coagulation disorders (D66-D69, O46.0, O67.0) Multifold pregnancy Cesarean sectio	In Denmark, it has since 2012 been mandatory to report the amount of blood lost during birth along with the O72 diagnosis.
PPH due to atony	ICD8: ICD9: ICD10: O72.1, and no trauma/retained tissue Post-2012 (DK only): ICD10: O72 (with >500mL blood loss), and no trauma/retained tissue	Known coagulation disorders (D66-D69, O46.0, O67.0) Multifold pregnancy Cesarean sectio	
PPH due to retained placenta	ICD8: ICD9: ICD10: O72.2 Post-2012 (DK only): ICD10: O72 (with >500mL blood loss) + O73	Known coagulation disorders (D66-D69, O46.0, O67.0) Multifold pregnancy Cesarean sectio	