

Supplementary information

ReproGen Consortium

Study	Lead investigators and analysts	Co-investigators
AGES (Age, Gene/Environment Susceptibility) Study	Tamara B. Harris, Albert V. Smith	Thor Aspelund, Gudny Eiriksdottir, Lenore J. Launer, Vilmondur Gudnason, Melissa Garcia, Michael Nalls
ARIC (Atherosclerosis Risk in Communities)	Nora Franceschini, Ellen Demerath	Aaron Folsom, Eric Boerwinkle, Maja Barbalic
CHS (Cardiovascular health study)	Anne Newman, Alice Arnold	Nicole Glazer, Barbara McKnight Bruce Patsy,
DeCode	Unnur Thorsteinsdottir, Patrick Sulem	Daniel Gudbjartsson, Simon N Stacey, Laufey Tryggvadottir, Unnur Styrkarsdottir, Kári Stefansson
ERF (Erasmus Rucphen Family) study	Cornelia M van Duijn, Sophie van Wingerden	M.Carola Zillikens, Najaf Amin, Ben A Oostra
EGPUT (Estonian Genome Project of University of Tartu)	Tõnu Esko, Andres Metspalu	Mari Nelis, Mari-Liis Tammesoo
FHS (Framingham Heart Study)	Joanne Murabito, Kathryn Lunetta	Douglas Kiel, David Karasik, Wei Vivian Zhuang
HAPI (The Heredity and Phenotype Intervention) Heart Study	Liz Streeten, Patrick McArdle	
InCHIANTI	Anna Murray, John Perry	Luigi Ferrucci, Stefania Bandinelli, Dena Hernandez Michael Weedon
NHS (Nurses Health Study)	Chunyan He, David Hunter	Peter Kraft, Susan E. Hankinson, Rob M. Van Dam, Marilyn C. Cornelis, Frank B. Hu
NTR (Netherlands Twin Register)	Dorret Boomsma, Jouke-Jan Hottenga	Gonneke Willemsen, Eco JC de Geus
QIMR (Queensland Institute of Medical Research)	M Byrne, Grant W Montgomery	Nicholas G Martin, Andrew C Heath
Rotterdam studies, RSI,II,III	Lisette Stolk, Jenny Visser, André Uitterlinden	Fernando Rivadeneira, Joyce van Meurs, Bert Hofman & Joop Laven
SardiNIA	Laura Crisponi, Mara Marongiu	David Schlessinger, Manuela Uda, Serena Sanna, Eleonora Porcu, Liana Ferrelì, Angelo Scuteri, Sandra Lai, Angelo Scuteri
SHIP (Study of Health in Pomerania)	Henry Völzke	Alexander Teumer, Henri Wallaschofski, Marek Zygmunt
TWINS UK	Massimo Mangino; Guangju Zhai, Tim D Spector	Andrea Burri, Nicole Soranzo
WGHS (Women's Genome Health Study)	Daniel I Chasman, Paul Ridker	Guillaume Paré, Kim Tsui, Alex Parker, Julie Buring

Supplementary Table 1. Association of GWAS menopause variants in early menopause and POF cases versus controls.

A. Excluding non-white individuals

SNP	Early menopause (Menopause <46) vs Controls				Early menopause excluding POF (Menopause 40-45) vs Controls				POF (Menopause <40) vs Controls			
	N	OR	95% CI	p value	N	OR	95% CI	p value	N	OR	95% CI	p value
rs4806660	3927	1.44	1.31-1.58	3.78 x10-15	3673	1.43	1.30-1.57	7.44x10-14	2133	1.51	1.26-1.83	0.000014
rs16991615	3884	1.86	1.52-2.27	1.06 x10-9	3629	1.98	1.60-2.45	2.62x10-10	2117	1.30	0.88-1.92	0.19
rs9379896	3937	1.14	1.01-1.28	0.03	3681	1.14	1.01-1.29	0.029	2140	1.09	0.86-1.40	0.47
rs244715	3307	1.20	1.09-1.33	0.00023	3095	1.22	1.10-1.35	0.00013	1800	1.10	0.89-1.35	0.37

B. Using conditional logistic regression to account for case/control matching

SNP	Early menopause (Menopause <46) vs Controls				Early menopause excluding POF (Menopause 40-45) vs Controls				POF (Menopause <40) vs Controls			
	N	OR	95% CI	p value	N	OR	95% CI	p value	N	OR	95% CI	p value
rs4806660	3502	1.46	1.32-1.61	2.18 x10-14	3076	1.43	1.29-1.58	9.10 x10-12	426	1.69	1.26-2.25	0.00037
rs16991615	3428	1.95	1.56-2.43	2.85 x10-9	2992	2.07	1.63-2.64	2.37 x10-9	436	1.34	0.76-2.36	0.32
rs9379896	3518	1.17	1.03-1.33	0.013	3074	1.19	1.04-1.36	0.011	444	1.06	0.75-1.50	0.73
rs244715	2480	1.25	1.12-1.39	0.000092	2164	1.23	1.09-1.39	0.001	316	1.37	1.01-1.85	0.045

Odds ratios are per risk allele.

Supplementary Table 2. Comparison of expected odds ratios for early menopause and POF based on the quantitative trait estimates from GWAS studies and the BGS controls.

Early Menopause (<46 years)												
SNP	BGS observed			ReproGen GWAS						Heterogeneity P BGS vs ReproGen	Published GWAS	BGS QT
	observed OR	95% CI	p value	beta	OR	lower CI	lower OR	Upper CI	upper OR		expected OR	expected OR
rs4806660	1.45	1.32 - 1.59	8.88×10^{-16}	-0.4062	1.20	-0.3474	1.17	-0.465	1.23	0.0001	1.25	1.12
rs16991615	1.85	1.51 - 2.25	1.45×10^{-9}	0.9709	1.57	0.848596	1.48	1.093204	1.67	0.1226	1.65	1.54
rs9379896	1.13	1.01 - 1.27	3.8×10^{-2}	0.2416	1.12	0.167708	1.08	0.315492	1.15	0.8834	1.14	1.06
rs244715	1.2	1.09 - 1.32	1.7×10^{-4}	0.2914	1.14	0.225936	1.11	0.356864	1.18	0.3171	1.19	1.03

POF (<40 years)												
SNP	BGS observed			ReproGen GWAS						Heterogeneity P BGS vs ReproGen	Published GWAS	BGS QT
	observed OR	95% CI	p value	beta	OR	lower CI	lower OR	Upper CI	upper OR		expected OR	expected OR
rs4806660	1.54	1.27 - 1.85	6.48×10^{-6}	-0.4062	1.35	-0.3474	1.29	-0.465	1.41	0.1818	1.44	1.21
rs16991615	1.3	0.88 - 1.92	0.18	0.9709	2.08	0.848596	1.90	1.093204	2.29	0.0216	2.25	2.01
rs9379896	1.06	0.84 - 1.35	0.61	0.2416	1.20	0.167708	1.13	0.315492	1.26	0.3178	1.24	1.09
rs244715	1.12	0.91 - 1.37	0.29	0.2914	1.24	0.225936	1.18	0.356864	1.30	0.3426	1.33	1.04