SUPPORTING ONLINE MATERIAL

Replicability and Robustness of GWAS for Behavioral Traits

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S-1. Educational Attainment Measure in Rietveld et al. (2013)

Rietveld et al. (2013) defines two measures of Educational Attainment (EA) in accordance with the 1997 International Standard Classification of Education (ISCED) of the United Nations Educational, Scientific and Cultural Organization. This classification transforms each country-specific educational system into seven internationally comparable categories of EA (UNESCO, 2006). In each study, EA of the participants was first transformed into the appropriate ISCED level of the country. Thereafter the equivalent to US years of schooling was calculated, as described in Table S1. In some countries the measures did not differentiate between levels 5 and 6. In these cases everyone with a tertiary education was coded as ISCED 5, and 20 years of schooling was coded instead of 19. The resulting continuous measure of EA as US-schooling-year equivalents is abbreviated as *EduYears* throughout the manuscript.

Rietveld et al. (Rietveld et al., 2013) also analyzes a binary outcome, *College*, which differentiates between individuals who hold a tertiary degree and those who do not. This binary variable was coded taking the value 1 if the individual had completed a college degree (ISCED level 5 or above of the ISCED classification), and 0 if the individual had not completed a college degree (ISCED level 4 or below).

EduYears may provide more information about individual differences within a country, but *College* may be more comparable across countries. Nonetheless, the point biserial correlation between the two measures is relatively high, e.g., 0.82 (in the STR sample). Note, however, that the *EduYears* analysis focuses on the effects at the mean of the phenotype distribution, whereas the *College* analysis focuses on differences between the upper tail of the phenotype distribution and the remaining values.

Analyses were performed using participants of European descent only (to help reduce stratification concerns). Educational attainment was measured after participants were very likely to have completed their education (over 95% of the sample was aged at least 30).

Table S1. ISCED classification scheme

ISCED Levels	Definition	US years-of-schooling equivalent (*EduYears*)	*College*
0	Pre-primary education	1	0
1	Primary education or first stage of basic education	7	0
2	Lower secondary or second stage of basic education	10	0
3	(Upper) secondary education	13	0
4	Post-secondary non-tertiary education	15	0
5	First stage of tertiary education (not leading directly to an advanced research qualification)	19	1
6	Second stage of tertiary education (leading to an advanced research qualification, e.g., Ph.D.)	22	1

S-2. Additional Methods for Study 1

S-2.1. Quality Control. The analyses are restricted to individuals of European ancestry in the 23andMe sample who have responded to survey questions about educational attainment. In order to include only individuals who are conventionally unrelated, we further restrict the sample such that no pair of participants shares more than 700 centimorgans of their genome identical-by-descent. Additional information about 23andMe data is available in Eriksson et al. (Eriksson et al., 2010).

S-2.2. Variable Definitions. In this dataset *College* is a binary variable equal to 1 if the participant reports having attended college. *EduYears* is coded similarly (but not identically to) the coding used by Rietveld et al. (Rietveld et al., 2013), as follows: 10 years of schooling for "Less than high school education"; 12 years of schooling for "High school"; 14 years of schooling for "Associate degree"; 16 years of schooling for "Bachelor degree"; 19 years of schooling for "Master or professional degree"; 22 years of schooling for "doctorate."

S-2.3. Analysis. As in Rietveld et al. (2013), we test for associations with *College* using logistic regression and with *EduYears* using linear regression. In all analyses, we control for sex, age, and the first 25 principal components (PCs) of the in-sample variance-covariance matrix of the genotyped SNPs (where entry (*j*, *k*) is the covariance between SNP *j* and SNP *k*). PCs were computed using all 23andMe customers who had 97% or more European ancestry as determined by a local ancestry method (similar to Falush et al., 2003), using the three HapMap populations as references. Overlaying individuals who reported four grandparents from the same country shows that this set includes people with ancestry from northern Europe, eastern Europe (including Finland, Russia, and the Baltics), southern Europe, as well as people with Near Eastern (e.g., Greece, Turkey) or Ashkenazi Jewish ancestry. See Figure S1 in Eriksson et al. (2010) for how self-reported ancestry correlates with the first 2 PCs in this sample. The PCs were computed using 91,859 SNPs that were selected to have MAF > 0.01, HWE $p < 1^{-40}$, call rate > 0.99, and be at least 1^{-4} cM apart from each other. The extremely low HWE cutoff was chosen because the statistics were calculated on well over 300,000 people.

Of the three education-associated SNPs identified in Rietveld et al. (2013), two (rs11584700 and rs4851266) are available in the 23andMe data. For the third, rs9320913, we use rs12206087—which is known to be strong linkage disequilibrium with it (R^2 = 0.99 in the 1000Genomes Phase I data)—as a proxy. The G allele of rs12206087 proxies for the C allele of rs9320913, while the A allele of rs12206087 proxies for the A allele of rs9320913.

S-3. Additional Methods for Study 2

S-3.1. Quality Control. The same quality control filters for QIMR and STR were used as in Rietveld et al. (2013). The QIMR (Medland et al., 2010) genotypes were assayed with three different chips, namely the Illumina 610, Illumina 370 and Illumina 317. SNPs were called using BeadStudio, and SNPs with a minor allele frequency (*MAF*) < 0.01, Hardy-Weinberg equilibrium (*HWE*) test $p < 10^{-6}$, and missingness > 0.05 were excluded from further analyses. The remaining SNPs were imputed with MaCH (Li, Willer, Ding, Scheet, & Abecasis, 2010) to the HapMap 2 reference panel (International HapMap Consortium, 2007). SNPs that did not reach an imputation accuracy of $R^2 > 0.3$ were also excluded.

In STR (Benjamin et al., 2012; Magnusson et al., 2013) the Illumina HumanOmniExpress-12v1_A with the GenomeStudio calling algorithm was used. SNPs with *MAF* < 0.01, *HWE p*

$< 10^{-7}$, and missingness < 0.03 were excluded. IMPUTE (Marchini, Howie, Myers, McVean, & Donnelly, 2007) was used to impute the genotypes to HapMap 2 and SNPs that did not reach an imputation accuracy of $R^2 > 0.3$ were excluded from further analyses. No genetic outliers were present in these data after quality control.

S-3.2. Variable Construction. *EduYears* and *College* in the dataset are constructed in the same way as in Rietveld et al. (2013). In QIMR three different educational scales were transformed to the ISCED scale, and in STR, data from Statistics Sweden containing the ISCED information for the year 2005 was used (see Rietveld et al. (2013) for further details). Polygenic scores were constructed as a linear combination of all imputed and directly genotyped SNPs that passed the quality control filters above, weighting each SNP with the regression coefficient from a meta-analysis that excluded the STR and QIMR samples such that the results of the meta-analysis were based on (All Cohorts minus QIMR) and (All Cohorts minus STR), respectively. The constructed polygenic scores were identical to those in Rietveld et al. (2013). As in Rietveld et al. (2013), the number of available SNPs for the *College* score is respectively 3, 113, 3,506, and 2,482,536 for *p*-value thresholds 5×10^{-8}, 5×10^{-5}, 5×10^{-3}, and 1; and for the *EduYears* score: respectively 5, 127, 3,369, and 2,484,855 for *p*-value thresholds 5×10^{-8}, 5×10^{-5}, 5×10^{-3}, and 1. In QIMR the number of SNPs included in the *College* score after quality control is respectively 3, 108, 3,301, and 2,352,773; the number of SNPs included in the *EduYears* score is 5, 125, 3,173, 2,352,772. In STR the number of SNPs included in the *College* score after quality control is respectively 3, 113, 3,506, and 2,482,515; the number of SNPs included in the *EduYears* score is 5, 127, 3,369, and 2,484,834.

S-3.3. Analysis. We regressed *EduYears* and *College* on these polygenic scores as in Rietveld et al. (2013), but now having first adjusted (via multiple regression) both *EduYears* and the score by the first 20 PCs estimated from the genotype data from the respective cohort. These PCs were computed in each cohort subsequent to all quality control steps. The adjusted R^2 from regressing *EduYears* on 20 PCs is 0.02 in the QIMR cohort (N = 3,544 unrelated) and 0.004 in the STR cohort (N = 6,770 unrelated).

We further performed a mixed-linear-model analysis (Kang et al., 2010) of *EduYears* on the polygenic score. This analysis controls for population structure by estimating the genetic relationship matrix (GRM) between individuals using all genotyped SNPs, and then modeling the covariance between any pair of individuals' *EduYears* as linearly increasing in the pair's

genetic relatedness. The GRM (where entry (*j*, *k*) is a scaled version of the in-sample covariance between individual *j*'s SNP genotype vector and individual *k*'s SNP genotype vector) captures population structure, cryptic relatedness, and all the real SNP effects. The analysis was performed in GCTA (Yang, Lee, Goddard, & Visscher, 2011).

S-4. Additional Methods for Study 3

S-4.1. Quality Control. Data from the Framingham Heart Study (FHS) come from the second (parental) and third (sibling) generation respondents. Genotypes were assayed using the Affymetrix GeneChip Human Mapping 500K Array and the 50K Human Gene Focused Panel. Genotypes were determined using the BRLMM algorithm and SNPs with *HWE* $p < 0.001$, missingness < 95%, and *MAF* < 0.05 were excluded. The screens were conducted using all available individuals with genetic data, not only those that were included in this analysis. We used the pruning command in PLINK (Purcell et al., 2007), setting the SNP window equal to 50, the number of SNPs to shift the window by at each step equal to 5, and a variance-inflation threshold of 2. Compared to Study 2, Study 3 used more stringent quality control filters and LD pruning. Furthermore, only directly genotyped data were available for Study 3 (whereas for Study 2 we had access to both directly genotyped data and imputed data). Consequently, the number of SNPs included in the polygenic score in Study 3 is much smaller than in Study 2. In particular, in Study 3, of the original 500,568 directly genotyped SNPs, 243,111 were left after quality control, LD pruning, and matching with the meta-analysis results of Rietveld et al. (2013).

After the quality controls were applied, we restricted the data to biological siblings. To do so, we proceeded in two steps. First, to construct "families," we identified all individuals whose mother ID and father ID codes are the same. Second, to remove pairs that are not full biological siblings, we subsequently conducted GCTA analyses (Yang et al., 2010) and removed any sibling pair outside the 40 percent to 60 percent IBD range. We define the remaining sample as the "sibling sample."

S-4.2. Variable Construction. Following Purcell et al. (2009), we constructed the linear polygenic score as a linear combination of the pruned SNPs, in which the weight of each SNP

is equal to the regression coefficient in the meta-analysis of Rietveld et al. (Rietveld et al., 2013).

S-4.3. Variable Definition. Education of the respondents was taken from self-report in Wave III and coded as highest grade completed (i.e., years of schooling), with a score of 12 for completion of high school, 16 for a bachelor degree, and a maximum of 21 for post-graduate work.

S-4.4. Analysis. Within the sibling sample we tested the score within-family by running regressions as described in the main text.

S-4.5. FHS Acknowledgment. The FHS data were obtained from the NIH GWAS repository (dbGaP), request #7909-7, project #2260.

S-5. Illustration of PCs Eliminating a Spurious Association

Following a referee's suggestion, we provide here an empirical example of how controlling for principal components can be an effective way of eliminating spurious associations, whereas controlling for self-identified "race" is not. For illustrative purposes, we use a polymorphism, the SNP rs3769005, that is known to be related to lactose intolerance via a known biological mechanism. Specifically, it is known to have correlation 0.9 (in the European samples from HapMap; The International HapMap Consortium, 2005) with the genotype of the gene *LCT* (the gene that codes for the enzyme lactase), which is perfectly associated with the phenotype of lactase persistence (Enattah et al., 2002). Because the SNP is known to vary substantially in frequency across groups (Bersaglieri et al., 2004), it is often used to illustrate population stratification. For example, it was found to be spuriously associated with height in an early study (Campbell et al., 2005). In the seminal paper that proposed using PCs to reduce population stratification (Price et al., 2006), it was shown that controlling for PCs eliminated spurious associations between this SNP and SNPs on other chromosomes which vary by ethnicity but which are not inherited jointly.

In our novel analyses here, we show that there is an association between the SNP rs3769005 and educational attainment when we do not control for any PCs, but this relationship evaporates when we add enough PCs as controls. Our analyses use data from the Health and Retirement

Study (HRS) (Juster & Suzman, 1995), an ethnically heterogeneous sample of Americans over the age of 50 for which genotypic data recently became available for a large subsample (N = 12,507) of respondents.

S-5.1. Quality Control. Genotyping quality control and final preparation of the HRS genotypic data were performed by the Genetics Coordinating Center at the University of Washington (Health & Retirement Study, 2012). These data were subsequently deposited in the NIH GWAS repository (dbGaP). We did not perform any additional quality control on the data. The genotypic data have been imputed to 1000 Genomes Phase I v3 by the University of Washington Genetics Coordinating Center (Health & Retirement Study, 2012). The SNP we focus on, rs3769005, is imputed with extremely high accuracy (R^2 = 0.996 in the 1000Genomes Phase I v3 data). Of the 12,507 genotyped individuals, 53 individuals were excluded from the imputation process due to missingness call rate greater than 2%. Thus, imputed data is available for 12,454 individuals.

S-5.2.Variable Definitions. We obtained the education data from the HRS datafile as prepared by RAND (RAND v.L, available at http://hrsonline.isr.umich.edu). This datafile contains harmonized variables across all waves of the study in which the data were collected. The education variable measures the years of education completed on a scale ranging from 0-17+ (in increments of 1 year). This variable is available for 12,403 of the 12,454 individuals with data on imputed genotypes.

The HRS also contains survey questions that ask respondents to categorize themselves as "White/Caucasian," "Black/African American," or "Other." We ran our analyses in two samples: the complete sample of genotyped HRS respondents (N = 12,403) and the subsample of respondents of who self-identify as White/Caucasian (N = 10,187). The principal components were therefore estimated separately for each sample. To construct the PCs, we used the software package GCTA (Yang et al., 2010, 2011), after imposing the recommended SNP filters of University of Washingston Genetics Coordinating Center and the additional removal of SNPs with a minor allele frequency < 1% and/or a Hardy-Weinberg p-value < 0.01.
S-5.3. Analyses. We estimate the following regression equations

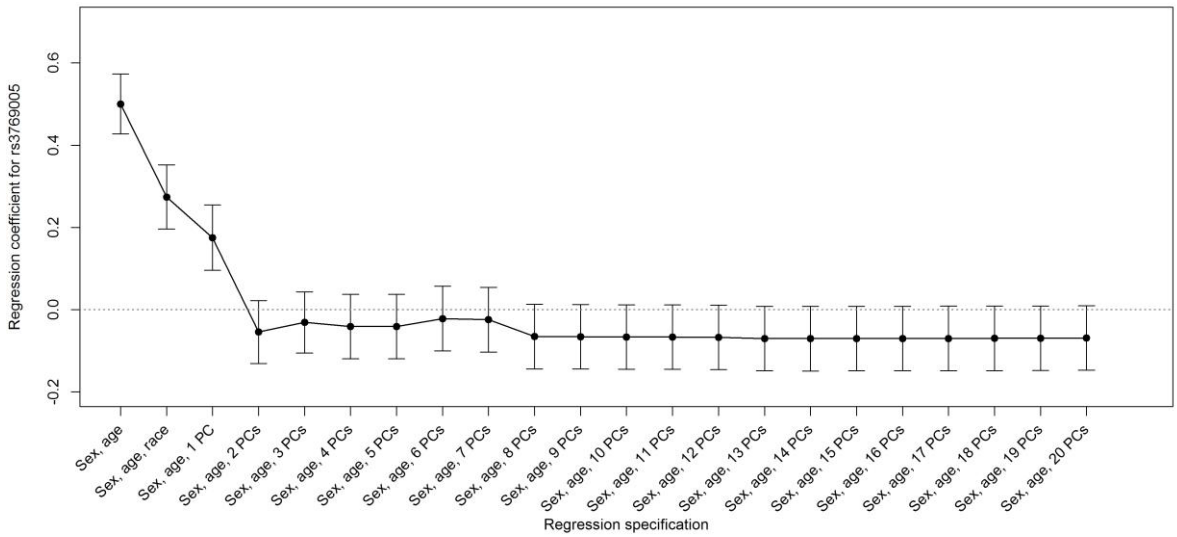
$$y_i = \mu + \beta x_{i,\mathrm{rs3769005}} + \boldsymbol{\gamma Z}_i + \epsilon_i,$$

where y_i is years of schooling; μ is a constant term; $x_{i,\text{rs3769005}}$ is the number of reference alleles individual i is endowed with at SNP rs3769005 (a continous variable due to the imputation, but always approximately equal to 0, 1, or 2); β is the coefficient of interest; and $\boldsymbol{Z}_i$ is a vector of controls. The vector always includes sex and age controls: specifically (following Rietveld et al., 2013), we control for sex, a cubic in age, and the interaction of sex with the cubic in age. However, we are primarily interested in seeing how the estimate of β changes as we progressively add more and more PCs as controls for population structure.

S-5.4. Results. The first column of Figure S1 ("Sex, age") shows that in the full sample, there is a very strong relationship between rs3769005 and years of education. The estimated coefficient is 0.500 years of schooling, approximately five times larger than the coefficients on the SNPs that reached genome-wide significance in Rietveld et al. (2013), and it is very precisely estimated. We believe that this association is almost certainly spurious because (a) the estimated effect size is much larger than one can plausibly expect for an individual SNP unless that SNP has a powerful and directly relevant biological effect, (b) the known biological effect of this polymorphism operates through lactose intolerance, which is unlikely to have a strong effect on educational attainment, and (c) the polymorphism is a prime candidate for strong population-stratification confounding since it varies greatly with ethnicity.

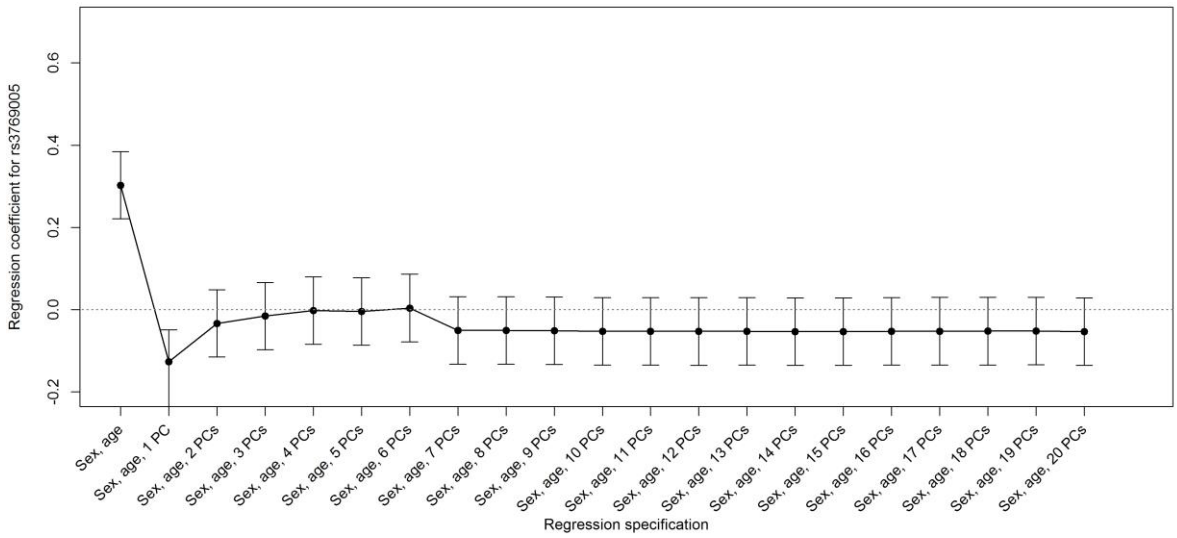
The second column ("Sex, age, race") shows that controlling for indicator variables describing the individual's self-identified race does not eliminate the association, though the estimated coefficient falls by approximately half, to 0.274 years of schooling. The remaining columns show how the coefficient changes as PCs are progressively added to the specification; the estimated coefficient stabilizes at -0.069 years of schooling after 8 or more PCs are included as controls, and it is never statistically distinguishable from zero once 2 or more PCs are included. To provide additional evidence on the strength of the association after PCs controls, we re-did Rietveld et al.'s (2013) meta-analysis of *EduYears* after excluding the HRS (which had contributed 8,626 individuals to the meta-analysis). The analysis plan had instructed each dataset to control for 4 PCs. In the remaining combined sample of 115,769 individuals, the coefficient for rs3769005 on *EduYears* is a statistically insignificant -0.0009 years of schooling with a standard error of 0.017.

Figure S1. Regression coefficient of rs3769005 with an increasing set of controls in the complete sample of genotyped HRS respondents (*N* = 12,403)



The results for only self-reported Whites are shown in Figure S2, which is analogous to S1 except that the specification with only sex, age and race is omitted (since of course none of the race indicator variables vary within this sample). The coefficient on *EduYears* is a statistically significant 0.302 years of schooling with only age and sex controls, becomes insignificant with 2 PCs, and stabilizes at a statistically insignificant -0.053 years of schooling once 7 or more PCs are included.

Figure S2. Regression coefficient of rs3769005 with an increasing set of controls in the subsample of genotyped HRS respondents who self-identify as White/Caucasian (*N* = 10,187)



These analyses suggest that controlling for a small number of PCs may be adequate to reduce population stratification concerns in genetic association analyses of behavioral traits. They also show that, in this example, controlling for self-reported race or restricting the analysis to Whites-only (which are the most common approaches to dealing with population stratification in candidate gene studies) is not sufficient.

S-5.3. HRS Acknowledgment. The HRS is supported by the National Institute on Aging (NIA U01AG009740). The genotyping was funded as a separate award from the National Institute on Aging (RC2 AG036495). The genotyping was conducted by the NIH Center for Inherited Disease Research (CIDR) at Johns Hopkins University.

S-6. Statistical Power Calculations

The statistical power estimates in the text are all obtained using Shaun Purcell's online statistical power calculator (Purcell, Cherny, & Sham, 2003). Throughout, we consider a polymorphism that explains 0.02% of the population variance of the phenotype, we set the significance threshold to 0.05, and we assume no dominance (i.e., a simple linear effect of the genotype on the phenotype).

S-6.1. Study 1. The power estimates for Study 1 are obtained using the "QTL Association for Sibships" calculator (http://pngu.mgh.harvard.edu/~purcell/cgi-bin/qtlassoc.cgi) with the "Singletons" option selected and the sample size set equal to 34,428 (the size of the 23andMe cohort). With this sample size, we calculate that our statistical power to detect a polymorphism at the 0.05 significance threshold that explains 0.02% of population variance is 75%.

S-6.1. Study 3. The power estimates for Study 3 are obtained using the same calculator but with the "Sibs" option selected. We set the sample size equal to 1,081, since this is the total number of unique combinations of pairs of siblings in our data. Notice that this number differs from the number of families (N = 589) included in the analyses: families with exactly two children contribute 2 pairs to the analyses, families with three children contribute exactly 3 pairs, and in general, families with n children contribute $\binom{n}{2} = \frac{n!}{2!(n-2)!}$ pairs to the analyses. Our sample includes 223 families with two children, 103 with three, 47 with four, 15 with five,

5 with six, and 2 with seven, as well as 194 families with a single child, which are omitted from this analysis. (Table 3 reports the number of families as $N = 395$ because we subtract the 194 families with a single child from the 589 total number of families in the sample.)

Since an exact power calculation would require a simulation study in order to take into account the variety of different family sizes in our sample, we instead take a simplified approach that is sufficient to make the point that our power is low for testing individual SNPs. Specifically, we assume that the 1,081 sibling pairs in our sample are drawn from 1,081 independent families. Doing so means that our calculation yields an upper bound for power because taking into account the correlation across sibling pairs within a family would reduce power.

Accordingly, we computed the statistical power using the "pairs" option in the power calculator. We assumed a sibling correlation of 0.4, which is the correlation in *EduYears* across siblings estimated in Rietveld et al. (2013), SOM section 2a and Table S11. Our upper-bound estimate of the statistical power to detect a polymorphism at the 0.05 significance threshold that explains 0.02% of population variance is 7%. Indeed, samples several orders of magnitude larger than ours would be required for a test of within-family association with a single SNP to have reasonable power: approximately 47,000 sibling pairs are required for 80% power.

S-7. Group banner for the Social Science Genetic Association Consortium (SSGAC)

The present paper builds on Rietveld et al.'s (2013) GWAS meta-analysis on educational attainment. The data used in Study 2 were accessed under section 4 of the Data Sharing Agreement of the SSGAC. Many of the authors who contributed to the Rietveld et al. (2013) paper also contributed directly to the present paper and are therefore listed as authors. Per SSGAC policy, remaining authors on the original GWAS meta-analysis are listed below as collaborators. The views presented in the present paper may not reflect the opinions of these collaborators.

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Smith, Gail Davies, Mariza de Andrade, Philip L. De Jager, Christiaan de Leeuw, Jan-Emmanuel De Neve, Ian J. Deary, George V. Dedoussis, Panos Deloukas, Jaime Derringer, Maria Dimitriou, Gudny Eiriksdottir, Niina Eklund, Martin F. Elderson, Johan G. Eriksson, Daniel S. Evans, David M. Evans, Jessica D. Faul, Rudolf Fehrmann, Luigi Ferrucci, Krista Fischer, Lude Franke, Melissa E. Garcia, Christian Gieger, Håkon K. Gjessing, Patrick J.F. Groenen, Henrik Grönberg, Vilmundur Gudnason, Sara Hägg, Per Hall, Jennifer R. Harris, Juliette M. Harris, Tamara B. Harris, Nicholas D. Hastie, Caroline Hayward, Andrew C. Heath, Dena G. Hernandez, Wolgang Hoffmann, Adriaan Hofman, Albert Hofman, Rolf Holle, Elizabeth G. Holliday, Christina Holzapfel, Jouke-Jan Hottenga, William G. Iacono, Carla A. Ibrahim-Verbaas, Thomas Illig, Erik Ingelsson, Bo Jacobsson, Marjo-Riitta Järvelin, Min A. Jhun, Peter K. Joshi, Astanand Jugessur, Marika Kaakinen, Mika Kähönen, Stavroula Kanoni, Jaakkko Kaprio, Sharon L.R. Kardia, Juha Karjalainen, Robert M. Kirkpatrick, Ivana Kolcic, Matthew Kowgier, Kati Kristiansson, Robert F. Krueger, Zóltan Kutalik, Jari Lahti, Antti Latvala, Lenore J. Launer, Debbie A. Lawlor, Sang H. Lee, Terho Lethimäki, Jingmei Li, Paul Lichtenstein, Peter K. Lichtner, David C. Liewald, Peng Lin, Penelope A. Lind, Yongmei Liu, Kurt Lohman, Marisa Loitfelder, Pamela A. Madden, Tomi E. Mäkinen, Pedro Marques Vidal, Nicolas W. Martin, Nicholas G. Martin, Marco Masala, Matt McGue, George McMahon, Osorio Meirelles, Andres Metspalu, Michelle N. Meyer, Andreas Mielck, Lili Milani, Michael B. Miller, Grant W. Montgomery, Sutapa Mukherjee, Ronny Myhre, Marja-Liisa Nuotio, Dale R. Nyholt, Christopher J. Oldmeadow, Ben A. Oostra, Lyle J. Palmer, Aarno Palotie, Brenda Penninx, Markus Perola, Katja E. Petrovic, Wouter J. Peyrot, Patricia A. Peyser, Ozren Polašek, Danielle Posthuma, Martin Preisig, Lydia Quaye, Katri Räikkönen, Olli T. Raitakari, Anu Realo, Eva Reinmaa, John P. Rice, Susan M. Ring, Samuli Ripatti, Fernando Rivadeneira, Thais S. Rizzi, Igor Rudan, Aldo Rustichini, Veikko Salomaa, Antti-Pekka Sarin, David Schlessinger, Helena Schmidt, Reinhold Schmidt, Rodney J. Scott, Konstantin Shakhbazov, Albert V. Smith, Jennifer A. Smith, Harold Snieder, Beate St Pourcain, John M. Starr, Jae Hoon Sul, Ida Surakka, Rauli Svento, Toshiko Tanaka, Antonio Terracciano, A. Roy Thurik, Henning Tiemeier, Nicholas J. Timpson, André G. Uitterlinden, Matthijs J.H.M. van der Loos, Cornelia M. van Duijn, Frank J.A. van Rooij, David R. Van Wagoner, Erkki Vartiainen, Jorma Viikari, Veronique Vitart, Peter K. Vollenweider, Henry Völzke, Judith M. Vonk, Gérard Waeber, David R. Weir, Jürgen Wellmann, Harm-Jan Westra, H.-Erich Wichmann, Elisabeth Widen, Gonneke Willemsen, James F. Wilson, Alan F. Wright, Lei Yu, Wei Zhao.

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