



Robust inference and correlates from genetic associations with personality

A full list of authors and affiliations appears at the end of the article.

Summary Paragraph

Personality traits describe stable differences in how people think, feel, and behave and how they interact with and experience their social and physical environments^{1,2}. Many questions remain unanswered about associations between DNA and personality traits, such as their robustness, generalizability, and the biological and social pathways through which they act. Here we meta-analyze data across 46 cohorts comprising 611K-1.14M participants with European-like and African-like genomes for genome-wide association studies (GWAS) of the Big Five personality traits (extraversion, agreeableness, conscientiousness, neuroticism, and openness to experience), and data from 51K participants for within-family GWAS. We identify 1,260 lead genetic variants associated with personality, including 824 novel variants³. Common genetic variants explain a moderate 4.8%–9.3% of the variance in measures of each trait, and 9.3%–13.3%

Reprints and permissions information is available at www.nature.com/reprints

*Correspondence should be addressed to tedschwaba@gmail.com, m.g.nivard@bristol.ac.uk, and tuckerdrob@utexas.edu.

**Lists of authors and their affiliations appear at the end of the paper

†M.G.N. and E.M.T-D. contributed equally to this work

Author Contributions

T.S., M.C.S., A.A., M.G.N., and E.M.T-D. conceived and designed the study and drafted and revised the manuscript. T.S., M.C.S., W.A.A., K.I., P.T.T., C.M.W., Y.D., T.T.M., J.D.T., W.L., L.S.A., J.C.M.F., and A.F.G. conducted analyses of meta-analytic data. T.S., K.I., T.T.M., J.D.T., W.L., P.G., M.B.S., J.G., D.F.L., U.Vösa., L.A., A.R., M.V., J.A., T.E., R.M., U.Vainik, G.A.J., G.T., A.F.G., G.B., T.E.T., H.Stefansson, K.S., R.C., Q.Q., E.C.C., H.A., F.A.T., E.Y., M.T., D.I.B., E.J.C.dG., J-J.H., D.C.M., H.Snieder, C.A.H., C.X., A.C., M.L., I.J.D., W.D.H., S-K.J., S.I.V., G.A., M.K.L., B.L.M., P.V.V., L.C-C., N.G.M., S.E.M., E.M.D., B.W., J.K., K.S., T.P., A.M., K.R., R.Plomin, M.M., D.M.D., F.A., L.W.W., F.U., M.A.M., H.R.K., Y.N., S.B., R.Polimanti, T.E., A.G., E.A.W., J.J.L., M.McGue, A.T., M.Marongiu, E.F., F.C., A.R.S., P.J.vdM., A.J.O., T.K., A.A.S., A.R.D., R.F.K., C.D.F., B.H.M., T.L., O.T.R., M.K., A.S., H.D., L.K-J., K.B., M.H-R., F.S., S.A., S.H.W., J.T., K.R., J.G.E., J.L., G.D., P.R., A.T., J.C., T.C.R., M.C., T.N., J.D., Y.Q., T.T., L.F., L.Z., L.S., K.P.H., E.G., P.D.G., S.G., C.F., J.E.S.P., S.L., A.S.M.H., C.S., S.C.H., A.A., M.G.N., and E.M.T-D. collected and conducted analysis of cohort-level data. G.H. and J.dlF. developed software used in the study. W.A.A., P.T., G.D.S., R.M., U.Vainik, G.A.J., T.E.T., R.C., E.C.C., H.A., F.A.T., N.G.M., E.M.D., J.K., L.W.W., R.Polimanti, A.T., P.J.vdM., C.X., M.L., I.J.D., W.D.H., H.D., F.S., L.F., K.P.H. provided iterative feedback on the manuscript and made substantial contributions to the interpretation of data. M.G.N and E.M.T-D. oversaw the study. All listed authors approved the final version of the manuscript.

Estonian Biobank Research Team

Tonu Esko⁵

⁵Institute of Genomics, University of Tartu, Tartu, Estonia. A full list of members and their affiliations appears in Supplementary Note 9.

COGA collaborators

Danielle Dick^{49,50}, Fazil Aliev⁵⁰

⁴⁹ Rutgers Addiction Research Center, Brain Health Institute, Rutgers University, Piscataway, United States. ⁵⁰ Department of Psychiatry, Rutgers Robert Wood Johnson Medical School, Piscataway, United States. A full list of members and their affiliations appears in Supplementary Note 9.

Spit for Science working group

Danielle Dick^{49,50}, Fazil Aliev⁵⁰

⁴⁹ Rutgers Addiction Research Center, Brain Health Institute, Rutgers University, Piscataway, United States. ⁵⁰ Department of Psychiatry, Rutgers Robert Wood Johnson Medical School, Piscataway, United States. A full list of members and their affiliations appears in Supplementary Note 9.

Competing Interest Declarations

No study authors declare any competing interests.

A FAQ on why, how, and what we studied is available at <https://osf.io/crh9d>

among instruments with typical measurement reliability. Genetic associations with personality are highly consistent but not identical across geography, reporter (self vs. close other), age group, and measurement instrument, and we find minimal spousal assortment for personality in recent history. In contrast to many other social and behavioral traits^{4,5}, within-family GWAS and polygenic index analyses indicate that genetic associations with personality are minimally confounded by the shared family environment. Polygenic prediction, genetic correlation, and Mendelian randomization analyses indicate that personality traits have widespread, potentially causal associations with consequential behaviors and life outcomes. Overall, we find that the genetic architecture of personality is robustly generalizable, minimally confounded, and widely relevant to human experience.

Introduction

Personality is defined by relatively stable patterns of thinking, feeling, and behaving that vary across individuals^{1,2}. Decades of research have demonstrated that human personality traits can be meaningfully and efficiently summarized by five relatively independent broad factors known as the *Big Five*: Extraversion (which encompasses traits such as sociability, assertiveness, and energy level), agreeableness (compassion, respectfulness, and trust), conscientiousness (organization, productiveness, and responsibility), neuroticism (anxiety, depression, and volatility) and openness to experience (imagination, curiosity, and aesthetic sensitivity)^{6–7}. Given personality's relevance to labor market outcomes^{8–10}, physical health^{10–12}, mental health^{13–14}, and human demography^{15–17}, understanding the molecular genetics of personality is important for developing biopsychosocial models of human behavior and life outcomes.

Here we report meta-analytic Genome-Wide Association Study (GWAS) results from the Revived Genomics of Personality Consortium (ReGPC), a collaboration across 46 cohorts incorporating between 611K and 1.14M participants per Big Five trait. We also provide a Frequently Asked Questions (FAQ) document that explains the rationale and results of this study in everyday language (<https://osf.io/crh9d>). This effort increases the number of significant loci relative to most recent work²² from 3 to 131 for conscientiousness, 4 to 39 for agreeableness, 8 to 126 for openness to experience, 14 to 258 for extraversion, and 224 to 706 for neuroticism. The additive effects tagged by the common genetic variants (h^2_{SNP}) account for an estimated 4.8%–16.2% of total personality variation across traits and models. This is in line with previous GWAS of personality^{3,18–21} and less than estimates of h^2 from classic twin and pedigree studies and molecular genetic methods that index effects of rare variants and genetic interactions, which range from ~40–60%^{22–25}. Critically, all methods find that personality is substantially influenced by a person's environment.

Our analyses reveal that genetic associations with personality traits are generalizable and minimally confounded, with widespread external correlates. Though personality traits often vary on average across groupings of people^{26,27}, we find that genetic associations with each trait are highly similar across four Western country clusters, reporter perspective (self vs. close other), age, and measurement instrument. Similarly, polygenic indices (PGIs) constructed from each primary GWAS predict personality consistently

across five independent cohorts. Biological characterization implicates trait-differentiated molecular and cellular systems of greater complexity than previously theorized^{28,29}. Within-family analyses indicate that, in contrast to GWAS of other behavioral traits^{4,5,30}, genetic associations with personality traits are only minimally confounded by population stratification, dynastic effects, and assortative mating. Finally, we characterize personality's wide-ranging genetic correlates and consequences across socially relevant behaviors and life outcomes ranging from psychopathology and physical health to research participation and residential mobility, highlighting a central role of personality in understanding the human experience.

Results

Population-level Meta-Analysis

We performed population-level GWAS meta-analysis of each Big Five trait in genetic-similarity-stratified and genetic-similarity-combined cohorts of participants with EUR-like ($k_{\text{cohorts}} = 46$) and AFR-like ($k_{\text{cohorts}} = 10$) genomes, as measured by genetic similarity to reference panels (Supplementary Tables S1–S3; Supplementary Notes 1–2). We jointly analyzed results using inverse-variance weighted meta-analysis (IVW), supplemented with Multi-Ancestry Meta Analysis (MAMA³¹), resulting in pooled associations for ~ 10 million Single Nucleotide Polymorphisms (SNPs) for each Big Five trait.

We identified 1,260 approximately independent ($r^2 < .10$ within a 250kb range) genome-wide significant (GWS; $p < 5 \times 10^{-8}$) SNPs associated with the Big Five traits, an increase of 3 to 43 times over the most recent findings for each trait (Table 1; Supplementary Tables S4–S13). Of the 1,260 lead SNPs, 824 (65%) were found in novel 250kb loci not previously associated with variation in the respective trait. Manhattan plots of IVW results are displayed in Figure 1 A–E. Demonstrating the independence between the Big Five, 82% of genomic loci containing a GWS SNP were associated with only a single trait (Supplementary Table S14), and the average absolute genetic correlation among Big Five traits among participants with EUR-like genomes was .19 (Figure 1 F, lower diagonal), similar to phenotypic correlations³² (Figure 1 F, upper diagonal).

Genetic effects were highly congruent when splitting EUR-like GWAS cohorts into two halves, re-estimating the GWAS in each half, and estimating genetic correlations between the two (mean $r_g = .94$) (Supplementary Table S15). Individual SNP effects were extremely small, reflecting personality's highly distributed genetic architecture. For example, the median association estimate among extraversion lead SNPs, corrected for the winner's curse³³, is .009 SD per effect allele (corresponding to scoring at the 50.35th vs 50th percentile in extraversion). On average, the estimated effective number of independently associated common SNPs for each trait was 16,180 (Supplementary Table S17). We present additional GWAS results, including genetic ancestry-stratified analyses and comparisons illustrating similarity between IVW and MAMA estimates, in Extended Data Figure 1 and Supplementary Tables S16–S20.

Characterizing SNP Heritability

Among participants with EUR-like genomes, SNP heritability (h^2_{SNP}) estimated for the Big Five traits using LD Score Regression (LDSC³⁴) ranged from 4.8% (SE = 0.2%) for agreeableness to 9.3% (SE = 0.3%) for extraversion (Table 1; Supplementary Table S4; Supplementary Note 3). Importantly, these SNP heritability estimates from GWAS meta-analysis index genetic effects that are consistent across contributing cohorts. To allow for variability in genetic effects across cohorts, we conducted a random-effects meta-analysis of cohort-specific h^2_{SNP} estimates, which indicated an average h^2_{SNP} of 8.6% (SE = 0.6%) across traits (ranging from 7.4% for agreeableness to 10.6% for extraversion; Table 1; Supplementary Table S21), with significant variability across cohorts (mean τ = 3.6%). Random response error by the participants cannot systematically relate to their genome.^{35,36} Accordingly, we found that personality measures with greater reliability (less random error) tended to be more heritable (b = 6.7%, SE = 0.7%; Extended Data Figure 2). In this analysis, the expected h^2_{SNP} for a measure of typical (median) reliability (α = .81) ranged from 9.3% for agreeableness (SE = 0.6%) to 13.3% for extraversion (SE = 0.6%), and h^2_{SNP} completely disattenuated for measurement error ranged from 10.8% for agreeableness (SE = 0.9%) to 15.8% for extraversion (SE = 0.9%; Table 1).

To further characterize the generalizability of genetic associations with personality, we examined the concordance of genetic signal across geography, age, veteran status, measurement instrument, and reporter perspective (Table 1; Extended Data Figure 3). Genetic effects were similar but not identical across four western country clusters (United States, Continental Europe, Nordic, and United Kingdom/Australia, mean r_g = .86, mean SE = .15), three age groups (young [≤ 25], middle [25–64] and older [65+], mean r_g = .80, mean SE = .18), between the Million Veteran Program and other, primarily non-veteran cohorts (mean r_g = .82, mean SE = .04), and across five personality measurement instruments (mean r_g = .85, mean SE = .07). Additional characterization of genetic architecture across measurement instruments using Genomic Structural Equation Modeling³⁷ confirmed that genetic effects plausibly operate at the level of broad cross-instrument latent factors, with only one locus showing significantly heterogeneous effects across measurement instruments (Supplementary Tables S22–S24, Extended Data Figure 4). Notably, genetic associations with agreeableness were less consistent across cohorts (Table 1), which explains in part why agreeableness exhibited lower heritability than other traits in the meta-analytic GWAS. In the Estonian Biobank, where participants' personality was assessed both by their self-report (N = 73,983) and reports by close others (N = 20,269), we found strong genetic overlap between rater perspectives (mean r_g = .84, mean SE = .12), indicating that the genetic architecture of personality is not an epiphenomenon of self-perception. In sex-stratified analyses of neuroticism in the UKB cohort, X-chromosome-linked h^2_{SNP} did not differ between males (N = 168,989; $h^2_{\text{SNP}, X}$ = .23%; SE = .04%) and females (N = 198,139; $h^2_{\text{SNP}, X}$ = .18%; SE = .03%; $p_{\text{difference}}$ = .33). The dosage compensation ratio ($\hat{\gamma}$ = 1.26, SE = .30) was intermediate between no compensation (.5) and full compensation (2.0) but was estimated relatively imprecisely. Genetic effects were correlated near-unity across sex (r_g = .96; 95% CI = [.81, 1.10]).

Biological follow-up of GWAS signal indicated that enriched gene-sets intersected across the Big Five (mean enrichment rank-order $\rho = .72$; Extended Data Figure 5), providing evidence for trait-overlapping molecular and cellular systems in personality neurobiology despite only modest genetic correlations (Figure 1 panel F). Consistent with theories of personality development that emphasize the prefrontal cortex^{38,39}, genetic associations for each Big Five trait except agreeableness were enriched in genes expressed in the prefrontal cortex (among these, top lead SNPs implicate *RCE1*, *FOXP2*, and *SEMA6D*, indicated in Figure 1; Supplementary Tables S25–S34). All traits demonstrated strong enrichment in protein truncating variant intolerant gene-sets specifically expressed in neurons (e.g., *ARNTL*, *TCF4*, *NEGR1*; Figure 1). This pattern suggests personality-relevant variants are under negative selection, which appears inconsistent with evolutionary theories that posit balancing selection mechanisms as responsible for maintaining genetic variation in personality^{40,41}. Neurobiological theories of the Big Five attribute dopaminergic etiology to variation in openness to experience and extraversion, and serotonergic etiology to variation in conscientiousness, neuroticism, and agreeableness^{28,29}. Based on sets of genes differentially expressed in specific brain cell types, both in mouse and human post-mortem tissues, we found little support for these hypotheses across trait-stratified tests: neither the effect size nor p -value placed serotonin or dopamine among the most enriched neuron types (Supplementary Tables S25–S29), suggesting their prominence in the literature relative to other types of neurons is not warranted.

Polygenic Prediction of Personality

We predicted personality traits in five independent cohorts using polygenic indices (PGIs). PGI weights were constructed using our EUR-like discovery GWAS with SBayesR⁴². In all Big Five traits in all five cohorts, PGIs significantly predicted their respective phenotypic personality trait among participants with EUR-like genomes (meta-analytic β ranged from .097 (.005) for agreeableness to .189 (.005) for extraversion; Figure 2A; Supplementary Tables S35–S36; Supplementary Note 4), representing an improvement in prediction over past research for extraversion, conscientiousness, and openness to experience^{3,43}. Highly consistent estimates across cohorts indicates a limited role of birth year, nationality, and ascertainment method in prediction accuracy.

We also predicted personality traits among participants with AFR-like genomes in the Add Health and HRS cohorts, again using weights constructed from the EUR-like GWAS. PGI prediction is expected to substantially decrease when there are differences in genetic ancestry between discovery and target samples⁴⁴. Nevertheless, PGIs significantly predicted extraversion (meta-analytic $\beta = .099$ (.016)), neuroticism ($\beta = .071$ (.017)), and openness to experience ($\beta = .047$ (.017)) at $p < .01$; Figure 2A; Supplementary Tables S35–S36), providing the first evidence for significant PGI prediction of personality traits beyond individuals with EUR-like genomes.

Associations with Behaviors and Outcomes

We quantified the relevance of personality genetics to relevant behaviors and life outcomes across tests of genetic correlation, PGI prediction, and Mendelian Randomization (MR) applied to EUR-like GWAS data (Supplementary Note 5). Genetic correlation and PGI

prediction results applied to AFR-like GWAS data are reported in Supplementary Note 5 and Extended Data Figure 6.

Genetic correlations: Genetic correlations estimated using LDSC indicate widespread genetic sharing between personality traits and health-relevant daily behaviors.

Conscientiousness in particular was genetically correlated with reduced substance use (across substances, mean $r_g = -.21$), greater sports frequency ($r_g = .35$), and greater preference for low-calorie foods ($r_g = .17$), as well as the likely downstream consequences of these behaviors: fewer spells in the hospital ($r_g = -.21$), healthier ageing ($r_g = .14$), and lower BMI ($r_g = -.16$) (Supplementary Tables S37–S38). Personality was also genetically correlated with fluctuations in accelerometer-measured behavior across the day, with openness to experience linked to increased night-time activity ($r_g \approx .25$) and conscientiousness to increased activity during the day ($r_g \approx .30$; Figure 2D).

We found substantial genetic correlations between the Big Five and each of 10 psychiatric disorders and 4 transdiagnostic psychiatric disorder factors (Figure 3). Genetic profiles associated with neuroticism were associated with increased risk for all forms of psychopathology (mean cross-disorder $r_g = .43$), particularly internalizing disorders (factor $r_g = .73$), whereas genetic profiles associated with agreeableness displayed cross-cutting protective associations (mean $r_g = -.20$). We also identified broad patterns of positive genetic associations between openness and psychopathology (mean $r_g = .20$), which are notably discrepant from the small and inconsistent associations commonly reported in phenotypic research^{13,14}. Many other personality-psychopathology associations were specific and differentiated: Extraversion genetics were associated with lower risk for internalizing disorders (factor $r_g = -.08$) but greater risk for neurodevelopmental disorders (factor $r_g = .18$), and conscientiousness genetics were associated with lower risk for neurodevelopmental disorders (factor $r_g = -.24$) but greater risk for compulsive disorders (factor $r_g = .13$). These findings provide strong support for close connections between personality traits and psychiatric disorders posited in psychiatric nosologies^{13,14}.

Genetic correlations between personality traits and survey behavior in the UK Biobank indicated links between personality and research participation (Figure 3). In particular, genetic variants associated with openness to experience and agreeableness were associated with completing optional questionnaires (mean $r_g = .22$; .11), whereas genetic variants associated with neuroticism were associated with fewer questionnaire responses ($r_g = -.23$) and more “*I don’t know*” and “*prefer no response*” answers (mean $r_g = .32$) after beginning a questionnaire. The genetics of personality may thus have a widespread, underacknowledged influence on sample composition and responses in published research that relies on survey data. In Supplementary Note 5.1, we further describe genetic correlation results from each of these nine outcome clusters.

PGI associations with outcomes: Genetic variants inherited at conception are expected to partially predict outcomes later in life via nondeterministic transactions with the environment^{46,47}. We examined PGI prediction of interviewer-rater qualities and delinquency in Add Health, a representative sample of young US adults (N = 5,110). We found that personality PGIs predicted how participants were perceived by their in-person

interviewer during data collection (Figure 2B; Supplementary Table S39): Those with PGIs reflecting lower neuroticism and higher extraversion, agreeableness, and openness to experience were more often perceived to have a more attractive personality, and those with PGIs reflecting higher agreeableness and conscientiousness were perceived to be more well-groomed. In a subsample of at-risk Add Health participants, personality PGIs were associated with a greater likelihood of delinquent behavior and intergenerational contact with the prison system, (Figure 2B; Supplementary Table S39): high polygenic propensity for neuroticism and low polygenic propensity for agreeableness had small-to-moderate associations with school suspension, running away from home, and ever pulling a knife or gun on another person.

Our socio-demographic analysis in UK Biobank (N = 419,261) linked personality PGIs to the characteristics of one's residence in later adulthood, controlling for place of birth to reflect residential mobility. Genetic profiles indicative of higher openness to experience predicted greater likelihood of moving into cosmopolitan professional areas and away from suburbia and challenged neighborhoods by middle-older adulthood (age 50+), whereas genetic profiles indicative of higher conscientiousness predicted greater likelihood of moving away from cosmopolitan areas and into affluent suburban communities (Figure 2E). We present additional residential mobility analyses focused on urban/rural migration in Extended Data Figure 7. These analyses substantiate theoretical associations between personality and life outcomes that have yet to be submitted to GWAS in large samples. Importantly, PGI prediction of behaviors and outcomes from personality-relevant genetic variants was small in magnitude. These PGIs cannot predict an individual's future behavior.

We also quantified personality similarity between spouses over recent generations. Inferred genetic correlations between parents, estimated using error-corrected PGI similarity meta-analyzed across spouses, sibling pairs, and cousin pairs from UK Biobank ($N_{\text{pairs}} = 187,703$) and deCODE ($N_{\text{dyads}} = 133,358$), indicated minimal assortative mating for each of the Big Five traits (Estimated parental $r_g = .01-.04$; Figure 2C; Supplementary Table S40). Over past generations, birds of a feather have not flocked together: parents were only minimally more genetically similar in their personality traits, on average, than would be expected by chance, and far less genetically similar than in educational attainment ($r_g = .37^{47,48}$). Phenotypic assortative mating estimates between deCODE parents ($N_{\text{pairs}} = 5,317$) were stronger in magnitude but remained small for all traits besides openness to experience ($r_s = .07-.12$; openness $r = .18$; Extended Data Figure 8; Supplementary Table S41), consistent with previous estimates⁴⁸.

Mendelian randomization: To test causality and directionality in associations between personality traits and biobehavioral outcomes, we applied Mendelian Randomization (MR) tests to a subset of 13 outcomes most likely to comport with core assumptions of this method (Supplementary Tables S42–S43). We found plausible causal effects for 33 exposure-outcome pairings, where effects directionally replicated across MR estimators and multiple 95% confidence intervals excluded 0 (Extended Data Figure 9). Twenty-four analyses indicated effects of personality on biobehavioral outcomes, providing novel evidence that personality traits affect physical health – for example, extraversion increased COVID infection risk, conscientiousness decreased BMI and reduced likelihood of smoking

initiation and frequency of spells in hospital, and neuroticism increased the likelihood of scoring lower on a healthy aging/longevity factor. Furthermore, in line with theoretical perspectives that life experiences affect personality development^{1,26}, we found nine plausibly causal effects of biobehavioral outcomes on personality, encompassing broad multi-trait effects of educational attainment, increased BMI, and smoking initiation on average levels of personality. Reassuringly, we found no evidence for MR associations between personality and three negative controls (birthweight, number of sisters, and number of brothers) that would only be associated with one's own personality through intergenerational confounding (residual gene-environment correlation). These tests provide valuable information on the potential causes and consequences of personality traits, which to date have been especially challenging to obtain using other methods⁴⁹. Nevertheless, future work should further triangulate the MR-based causal inferences reported here with additional methods and data that permit strong causal inference⁵⁰.

Evaluating Familial Confounding

Polygenic prediction within families: We used data from the Netherlands Twin Registry ($N_{\text{families}} = 2,956$) and Twins Early Development Study ($N_{\text{families}} = 4,751$) to predict personality traits within dizygotic twin pairs. These models predict personality from twin *differences* in PGIs constructed from the primary EUR-like population GWAS. By holding family environment and parent genotype constant, and leveraging the randomness of intergenerational genetic transmission, these within-family comparisons substantially reduce genetic confounding that may be present in population-level GWAS^{4,5,51,52} (Supplementary Note 6).

For all Big Five traits in both cohorts, within-twin-pair PGI differences predicted the respective personality trait, with indistinguishable magnitude from population-level PGI prediction. The average within-family effect (β), meta-analyzed across the NTR and TEDS cohorts and averaged across the Big Five, was $\beta = .159$, compared to $\beta = .165$ for the population-level effect (a prediction ratio of 96%; Figure 4B; Supplementary Tables S35–S36). This similarity suggests negligible familial confounding in population-level genetic associations with personality. This result contrasts starkly with the notable within-family attenuation found for other behavioral traits, such as educational attainment (mean within/population predictive ratio ~60%^{4,5,53}), cognitive ability (~80%^{4,5}), and externalizing psychopathology (~75%²¹).

We further tested for familial confounding using a complementary method that is expected to be less biased by potential effects that siblings may have on one another⁵². We leveraged parent-offspring data from deCODE ($N = 34,506$) to decompose population-level PGI prediction into direct effects (genetic variants passed down from parent to offspring) and familial confounds (parental genetic variants not transmitted to the offspring, population stratification, and assortative mating). Across the Big Five, direct effects accounted for an average of 96.2% of variance in in population-level PGI prediction (Figure 4; Supplementary Table S44), indicating that genetic associations with personality operated nearly exclusive through direct transmission from parent to offspring. The identity of these results to those of within-twin PGI analyses indicates negligible confounding from effects that siblings

have on one another. Only for conscientiousness were non-transmitted genetic confounds significantly predictive of offspring personality (explaining 8.1% of the total predicted effect, indirect effect $B = .015$, 95% CI = [.003, .027], $p = .01$). Non-transmitted confounds did not differ in magnitude across mothers and fathers (Supplementary Table S45). In comparison, for educational attainment, only 75.1% of variance was explained by direct effects (indirect effect $B = .069$, 95% CI = [.055, .083], $p = 3.3 \times 10^{-21}$; Supplementary Table S44). After controlling for familial confounds, PGI prediction of extraversion by the extraversion PGI ($B = .207$) was similar in magnitude to PGI prediction of educational attainment by the educational attainment PGI⁵³ ($B = .208$). Overall, these tests rule out large or moderate effects of familial confounding in genetic associations with personality; they indicate that such effects are negligible to small in magnitude.

Within-family genome-wide analyses: As a test of familial confounding at the level of individual SNPs^{5,52}, we conducted within-family GWAS for each Big Five trait. We assembled data across 12 contributing EUR-like cohorts ($N = 31,544$ – $50,725$ across traits) that ascertained genetic data among family members using best-practices quality control³⁶ combined with published within-family GWAS estimates of Neuroticism³⁵ (Supplementary Table S46; Extended Data Figure 10).

LDSC-estimated h^2_{SNP} from within-family GWAS ranged from 7.6% (SE = 1.6%) for agreeableness to 13.4% (3.2%) for openness to experience, evincing comparable magnitudes to those reported for the complete meta-analyses of population GWAS (Figure 4; Supplementary Table S47). To maximize comparability between within-family and population-level GWAS, we also estimated h^2_{SNP} using meta-analysis of population-level GWAS among the matched subset of 12 cohorts who contributed to the within-family GWAS (Figure 4). For each trait, LDSC within-family intercepts were lower than population-level intercepts, suggesting these models accounted for residual confounding in population-level models.

h^2_{SNP} comparisons across models, using $p < .05$ as a significance threshold to maximize identification of potential differences, indicated that for only openness to experience were matched population-level h^2_{SNP} estimates significantly greater than within-family h^2_{SNP} estimates (19.4%; 95% CI[15.8%, 22.9%] vs 13.4%, 95% CI[7.1%, 19.6%], $p = .02$). This observed difference was driven largely by an inflated population-level h^2_{SNP} estimate for openness to experience in the Estonian Biobank sample (Supplementary Table S46). In contrast, previously-reported comparisons for other social and behavioral traits, such as educational attainment, depression, and household income, indicate LDSC h^2_{SNP} is attenuated by up to ~50% in within-family data³⁶. LDSC-estimated genetic correlations between within-family and population-level GWAS summary data averaged $r_g = .86$ and were significantly less than 1.00 only for neuroticism ($r_g = .75$, 95% CI[.61, .90], $p < .001$) and agreeableness ($r_g = .79$, 95% CI[.61, .97], $p = .03$). These results indicate strong correspondence in genetic effect estimates between population-level and within-family analyses, but we note generally wider confidence intervals, indicating a need for additional within-family GWAS data collection. Further comparisons across non-overlapping cohorts indicated that population-level and within-family effect sizes for significant and suggestively-associated SNPs ($p < 1 \times 10^{-5}$) were highly comparable in

magnitude, demonstrating that uncontrolled confounding in population-level GWAS is small in magnitude and that genetic associations with personality are replicable (Supplementary Note 6.7, Supplementary Table S47).

Genetic correlations between these within-family Big Five summary statistics and the 85 population-level external GWAS phenotypes were similar but not identical to fully population-level genetic correlations (mean correlation among r_g estimates = .83; Supplementary Table S48; Extended Data Figure 10). Fully within-family genetic correlations between these summary data and 18 phenotypes from [40] were also highly similar to population-level genetic correlations, despite notably less power (mean r between r_g estimates = .87; Supplementary Table S49; Extended Data Figure 10).

Discussion

In a consortium effort assembling data from 46 cohorts covering 611K–1.14M participants, we conducted highly-powered GWAS of each of the Big Five personality traits, establishing a rigorous basis for inference in personality genomics and highlighting the fundamental role of personality in the human experience.

Genetic and environmental factors, along with their correlations and interactions, contribute to variation in personality^{36,37,23,24}. We estimated h^2_{SNP} at 4.8%–9.3% using population-level data and 7.6–13.4% using within-family data. As expected from psychometric theory, heritability estimates were higher when personality was measured using more reliable instruments, revealing a predictable tradeoff between reliability (longer tests) and larger samples that should factor into future data collection. Notably, our h^2_{SNP} estimates, which only index effects of common genetic variants, are markedly lower than the 40–60% heritability estimates produced by twin and family methods^{22,23} and molecular genetic methods that more completely incorporate effects of rare variants and genetic interactions^{24,25}.

Comparisons of population-level and within-family associations indicated that genetic associations with personality are *relatively unconfounded* by assortative mating or by environmental factors that are shared across family members, including uncontrolled population stratification and dynastic effects⁵¹. This result contrasts with those obtained for other social science traits, such as educational attainment, income, externalizing behavior, and cognitive performance^{4,5,21,51,53}, for which genetic associations are substantially attenuated in within-family analyses compared to population-level analyses. However, confounding was not entirely absent, and even small confounding effects can be meaningful. For agreeableness and neuroticism, within-family and population GWAS effect estimates were genetically correlated at less than unity. For openness to experience, h^2_{SNP} from within-family GWAS was significantly lower than from matched-sample population GWAS (but not full population GWAS), and for conscientiousness, non-transmitted parental alleles had a small but significant contribution to PGI prediction. Finally, highly powered analyses of assortative mating identified effects that were significant but very small in magnitude. Collection of additional within-family data will provide further leverage to accurately and precisely identify loci indexing direct genetic effects. Importantly, even direct genetic

effects do not determine an individual's personality. Rather, genetic associations act probabilistically across large samples of people⁵⁴, and may interact with and operate through environmental experiences⁴⁶.

Genetic associations with personality largely *generalized* across different regions of Western geography, age groups, self-rated versus other-rated report, military service vs. general population samples, and measurement instrument. This suggests that widespread genetic inference is possible, even though the mechanisms linking genetic variation to personality trait differences are numerous, dynamic, and complex. One key departure from this overall pattern pertains to agreeableness, which exhibited lower genetic correlations across geography and rater instrument, suggesting that genetic effects relating to this trait may be more varied across groups and/or measurements, and inference must be more contextualized. In the future, finer-grained analyses, stratified by sex, age, and more expansive ancestral and cultural backgrounds, will further refine inferences about the differentiation of personality genetics across environments.

Functional genomic analyses and biological annotation indicated that despite their only modest genetic intercorrelations, genetic associations with each of the Big Five occur via overlapping molecular and cellular systems. Single cell gene expression data integrated with our GWAS indicated that there is no straightforward reductive mapping from broad, multifaceted personality traits to specific neuron types or neurotransmitters. These analyses did not fully align with preexisting theories that specifically link serotonergic, and dopaminergic neuronal processes to personality^{28,29}. However, the availability of these high powered GWAS combined with ever-expanding access to temporal and spatial brain gene expression data will enable future developmental and system-specific analysis of personality etiology.

Much of the scientific value of studying personality stems from its applicability to nearly all aspects of human life^{6–17}. We extend this tenet by linking heritable variation in personality traits to core mental and physical health outcomes, labor market performance, and reproduction, as well as specific behaviors like survey response, lifespan residential mobility, and impressions made on others. Causal inference in these associations is especially valuable, given that personality traits are highly stable over time²⁶ and resistant to simple experimental manipulation⁴⁹. MR results implicate personality traits as both potential causes and consequences of a range of health conditions. Given personality's pervasive relevance, researchers across scientific fields will benefit from incorporating personality traits when predicting and explaining biopsychosocial outcomes.

Online-Only Methods

Cohorts and Measures

We incorporated personality trait data from 46 cohorts participating in the Revived Genomics of Personality Consortium (ReGPC). Cohorts were included that provided data on genotyped participants with EUR-like and AFR-like genomes who had completed a validated multi-item personality inventory compatible with the Big Five personality trait taxonomy. Descriptive statistics for each cohort are provided in Supplementary Tables S1

and S2. Descriptions of each cohort are provided in Supplementary Note 7. A PRISMA flowchart for this meta-analysis is available at <https://osf.io/sh8gr>. These analyses were not pre-registered. As this meta-analysis used de-identified summary-level data, it was deemed exempt from ethics board approval by the University of Texas at Austin Institutional Review Board (STUDY00001941); ethics approval for individual cohorts that collected data and contributed to the meta-analysis is presented in Supplementary Note 7. All participants consented to the research, and this research was performed in accordance with all relevant guidelines and regulations.

Population-Level Meta-Analysis

For each trait, in each cohort, we conducted population-level genome-wide association analyses among participants with EUR-like and AFR-like genomes⁵⁵ across the 22 chromosomes and the X chromosome, following a standard operating procedure (<https://osf.io/rsc49>). In each cohort, we excluded SNPs with in-sample Minor Allele Frequency (MAF) < 1%, Call rate < 95%, deviation from Hardy-Weinberg Equilibrium ($p < 1 \times 10^{-5}$), poor imputation quality (INFO < .40), and those with poor clustering on visual inspection of intensity plots. Participants were excluded if they had low overall call rates (< 95%), excess autosomal heterozygosity or homozygosity, were duplicated samples, had gender inconsistent with sex (which is often indicative of mislabeled demographic data⁵⁶), or had chromosomal abnormalities. Association analyses were conducted in each cohort by regressing personality trait score on each biallelic 1000 Genomes 3v5 EUR or AFR SNP⁵⁷ with PLINK2⁵⁸, PLINK⁵⁹, GCTA⁶⁰, BOLT-LLM⁶¹, FastGWA⁶² or proprietary software, using mixed models to account for relatedness when appropriate. These analyses included controls for age, age², birth cohort, sex, and genetic principal components, to address potential lifespan and birth cohort differences in personality traits^{1,26}. Some groups contributed separate results for potentially-overlapping cohorts of participants. In these cases, we meta-analyzed estimates while accounting for dependency of their estimation errors. We harmonized and directionally aligned effects using EasyQC⁶³ and checked that effects were directionally consistent across cohorts by estimating genetic correlations with LDSC³⁴ (conducted on HapMap3 SNPs with an INFO threshold of $\geq .90$) in GenomicSEM³⁷.

For each Big Five trait, we then conducted inverse-variance-weighted (IVW) meta-analysis of GWAS estimates across all contributing cohorts, separately for participants with EUR-like and AFR-like genomes, in R 4.3.1⁶⁴. For each meta-analyzed SNP, we re-estimated N using observed meta-analytic MAF and standard error. This produced 10 sets of summary statistics (five traits $\times$ two ancestral groups). We quantified the number of genome-wide significant lead SNPs at $p < 5 \times 10^{-8}$ that were LD-independent of other lead SNPs nearby on the genome (within a 250kb window) using FUMA⁶⁵. We also identified lead SNPs that were LD-independent of all other lead SNPs on the chromosome regardless of genomic distance. Ancestry-stratified Manhattan plots of meta-analytic genome-wide associations are presented in Extended Data Figure 1.

We then conducted transancestry IVW meta-analyses to synthesize data across the $k = 10$ cohorts that included participants with both EUR-like and AFR-like genomes, and

the additional $k = 36$ cohorts including solely participants with AFR-like genomes. Because ~95% of participants were of European-like ancestry, and because stronger linkage disequilibrium among EUR-like compared to AFR-like superpopulations⁶⁶ means that employing the EUR reference panel likely leads to conservative estimation of the number of lead SNPs, we initially identified candidate lead SNPs using the 1000 Genomes 3v5 EUR reference panel. Using information on SNP LD from the 1000 Genomes 3v5 EUR and AFR reference panels, we estimated transancestry sample-size weighted LD matrices for each chromosome across all candidate transancestry lead SNPs and all lead SNPs from the ancestry-stratified analyses, which we used to identify additional LD-independent lead SNPs. To supplement transancestry IVW results, we also conducted transancestry meta-analyses using MAMA³¹.

We tested consistency of genetic signal across cohorts by splitting the 46 EUR-like discovery cohorts into two balanced halves, conducting IVW meta-analyses separately in each half, and using LDSC to test the concordance of genetic signal across split halves. We identified novel lead SNPs in the current GWAS relative to past GWAS as those that were outside the same 250kb locus as or LD-independent of a significant SNP in past GWAS of the Big Five. Finally, we quantified similarity in genetic signal among the Big Five by identifying overlapping 250kb genetic loci across pairs of traits and by estimating genetic correlations between pairs of Big Five traits using LDSC.

Characterizing SNP Heritability

We estimated h^2_{SNP} for each personality trait using LDSC. Because LDSC requires ancestrally-homogenous data, we applied this method separately to GWAS summary statistics of participants with EUR-like genomes, AFR-like genomes, and, for comparison purposes, EUR-like genomes in the subset of 10 cohorts that ascertained participants with both EUR-like and AFR-like genomes. We estimated polygenicity using Stratified LD Fourth Moments Regression⁶⁷, and we estimated within-trait transancestry genetic correlations using POPCORN⁶⁸.

We additionally applied LDSC to GWAS data on each individual cohort and then meta-analyzed h^2_{SNP} estimates across cohorts using fixed-effects and random-effects meta-analyses, with the R package metafor⁶⁹. To quantify the effect of measurement error of the personality measure on h^2_{SNP} , we conducted meta-regressions, where h^2_{SNP} in a cohort was regressed on the Cronbach's alpha reliability of its personality measure (reliabilities are presented in Supplementary Table 1). For each trait, we also used LDSC to correlate genetic effects across each pair of cohorts with positive h^2_{SNP} estimates (1,781 total pairings) and used fixed-effects meta-analysis to obtain an average estimate for this cross-cohort genetic correlation.

To quantify the consistency of genetic signal in each of the Big Five across groups, we sorted EUR-like cohorts by five grouping variables with substantial variation and $N > 10,000$ per group: geographic region (US, UK/Australia, continental Europe, and Nordic), age group (most participants <25, 25–64, and 65+ years), rater perspective (self-report and other-report, with data for these comparisons contributed exclusively from the Estonian Biobank cohort), military veteran status (MVP cohort participants and participants

from all 45 other cohorts), and measurement instrument family (Big Five Inventory^{70–72}, NEO Personality Inventory^{73–77}, International Personality Item Pool inventories^{78,79}, 100 Nuances of Personality Inventory⁸⁰, and Eysenck Personality Inventory^{81,82}). We then estimated genetic correlations across groups using bivariate LDSC. Finally, we compared X-chromosomal associations with neuroticism across males and females in the UK Biobank cohort, estimating h^2_{SNP} , cross-sex r_g , and the dosage compensation ratio^{83,84} on sex-stratified summary data of unrelated males (N = 168,856) and females (N = 197,927) with EUR-like genomes.

We applied GenomicSEM to formally model the genetic factor structure of the different measurement instruments and to compute the Q_{SNP} statistic, which quantifies the extent to which SNP associations with each instrument varied beyond what would be expected under the factor model⁸⁵. We specified a five-factor model in which each instrument served as an indicator of its respective Big Five trait and cross-loadings were added based on an iterative data-driven approach. For each SNP, we computed the Q_{SNP} statistic by comparing a model in which each factor was regressed on the individual SNP to one in which all specific measurement instruments were regressed on the individual SNP.

To identify annotations enriched for h^2_{SNP} , we submitted each of the five EUR-like GWAS summary statistics to MAGMA⁸⁶, including SNPs with $\text{INFO} \geq .80$. The gene sets included in this analysis came from Akingbuwa and colleagues⁸⁷. We then indexed the similarity of enrichment across the Big Five using pairwise rank correlations of enrichment effect sizes from these analyses.

Polygenic Prediction of Personality

We generated polygenic index (PGI) weights for each Big Five trait by applying SBayesR⁴² to EUR-like GWAS estimates for the set of 1.3 million HapMap3 SNPs. PGI weights for each of the Big Five were then used to construct PGIs in five cohorts: the National Longitudinal Study of Adolescent to Adult Health (Add Health), German Socioeconomic Panel (GSOEP), Health and Retirement Study (HRS), Netherlands Twin Register (NTR), and Twins Early Development Study (TEDS). Each cohort ascertained participants with EUR-like genomes, and Add Health and HRS also ascertained participants with AFR-like genomes. As HRS, NTR, and TEDS also contributed to population-level GWAS, we held data from each respective cohort out when estimating PGI weights in that cohort, to prevent overlap in training and prediction sets.

We used each of these PGIs to predict the corresponding Big Five trait in each cohort. We estimated *population-level* effects using ordinary least squares regression for cohorts of unrelated participants (Add Health, GSOEP, and HRS) and linear regression with cluster-robust standard errors across families to account for relatedness in cohorts of twins (NTR and TEDS). These regressions controlled for age, age², sex, 10 ancestral principal components, and genotyping batch effects, with significance set at $p < .01$. We also generated PGI weights both among a broader set of 2.9 million SNPs and using PRS-CSx⁹⁴, and we compared this prediction to prior estimates. As we describe further in the Supplementary Note 4, these changes did not improve prediction, so we focus on analyses using SBayesR and the set of 1.3m HapMap SNPs.

Associations with Behaviors and Outcomes

We quantified genetic correlations between the Big Five and 85 external phenotypes that had previously been submitted to GWAS, among participants with EUR-like genomes, using LDSC. For 13 of these phenotypes, GWAS data were available to also estimate these genetic correlations among participants with AFR-like genomes. We set the significance threshold at $p < .01$ for these analyses. Outcomes and their source GWAS are presented in Supplementary Table 37.

We also used PGIs to estimate associations between the Big Five and 19 phenotypic behaviors and outcomes that have not been submitted to GWAS and thus could not be analyzed with LDSC. To do this, we adapted the method described above in **Polygenic Prediction of Personality** to predict each behavior/outcome from each of the Big Five PGIs across participants. In residential mobility PGI analyses, we included statistical controls for place of birth (so that effects reflect residential movement), median home prices (to control for affordability), age, sex, and 5 principal components. We further filtered results only to those that directionally replicated within-family, to reduce potential confounding (see **Evaluating Familial Confounding** below) and applied the false-discovery rate correction⁸⁹.

We quantified assortative mating in personality over recent generations using a method that disattenuates PGIs for measurement error, enabling the estimation of genetic correlations across family members. Specifically, we estimated two independent sets of PGI weights for each participant, one from each split-half GWAS (see **Population-Level Genome Wide Association Analyses** above). We then estimated a structural equation model in the R package lavaan⁹⁰ that used the two PGIs as indicators of a latent, measurement-error-free PGI for each participant³⁶. We correlated these PGIs across pairs of spouses, siblings, and cousins in the UK Biobank and deCODE cohorts (see Extended Data Figure 8 Panel B for a path diagram of this latent correlation model). PGI correlations between members of spousal dyads in this model directly estimate genetic assortative mating. For siblings and cousin dyads, we transformed PGI correlations to be on the same scale as spouses. We then used IVW meta-analysis to synthesize these estimates across relationship types and the two cohorts.

We conducted Mendelian Randomization (MR) analyses to examine putatively causal bidirectional effects between personality traits and external phenotypes, using the R package TwoSampleMR⁹¹. For these tests, we selected 13 external behaviors and outcomes from the broader pool of 85 on the basis of previous personality theory (Supplementary Note 5.5). We also selected three phenotypes to serve as negative controls (birthweight, number of sisters, and number of brothers), as these cannot be directly caused by an individual's personality. For each phenotype, we conducted MR tests using three estimators chosen for their complementarity and robustness to common violations of MR assumptions⁹²: weighted mode with Steiger filtering⁹³ weighted median with Steiger filtering⁹⁴, and MR-CAUSE⁹⁵. To identify replicable effects in the context of multiple tests, we considered an effect to be significant only if estimates were directionally consistent across all three MR methods with unadjusted 95% confidence/credibility intervals that excluded 0 across at least two methods.

Evaluating Familial Confounding

To evaluate familial confounding in population-level PGIs, we compared population-level PGI prediction to *within-family PGI prediction*: the prediction of phenotypic variation in personality traits from variation in genotype, controlling for the genotypes of one's family members. For both the NTR and TEDS cohorts, we constructed PGI weights from the primary EUR-like population GWAS meta-analysis, excluding the respective twin cohort used for PGI prediction. We then estimated within-family PGI associations among dizygotic twin pairs, controlling for family-level fixed effects, as well as sex, age, and age². We pooled estimates across the two cohorts and compared them to pooled population-level PGI estimates to obtain an index of residual confounding in population-level PGIs.

We then estimated within-family PGI prediction in the deCODE cohort, in which parent-offspring units were each genotyped. In this cohort, we predict an offspring's personality trait from their PGI, controlling for their mother's PGI, their father's PGI, sex, age, age², and their county of birth. For each trait, we obtained estimates of the population-level effect (the total prediction) and the indirect genetic confounding (the contribution to prediction made by parental PGI scores, both together and separately by mother and father), and we estimated the direct genetic effect by subtracting the indirect genetic confounding from the population-level effect. To provide a point of comparison, we repeated this within-family PGI prediction using the phenotype of educational attainment. Educational attainment PGI weights were estimated in SBayesR following the procedure used for the Big Five, using GWAS summary data from [53] that excluded the 23&Me and deCODE cohorts.

We also conducted within-family GWAS analyses on EUR-like participant cohorts ($k = 12$) that ascertained genomic and personality data among family members. In each cohort, analysts estimated population-level and within-family effects for each SNP on each Big Five trait using either snipar³⁰ or the pipeline developed by Howe and colleagues⁴. For these analyses, we conducted stringent QC, including only SNPs with imputation INFO $\geq .99$ and correcting downwardly-biased h^2_{SNP} estimates in small samples (Supplementary Note 6.3), and we pooled effects across cohorts with IVW meta-analysis. For neuroticism, we incorporated additional previously-published summary data⁴. For each SNP, sample size was re-estimated using the meta-analytic standard error and 1000 Genomes 3v5 MAF, capped at the 75th percentile of the summed observed sample size across contributing cohorts. This method produced within-family summary statistics for each of the Big Five.

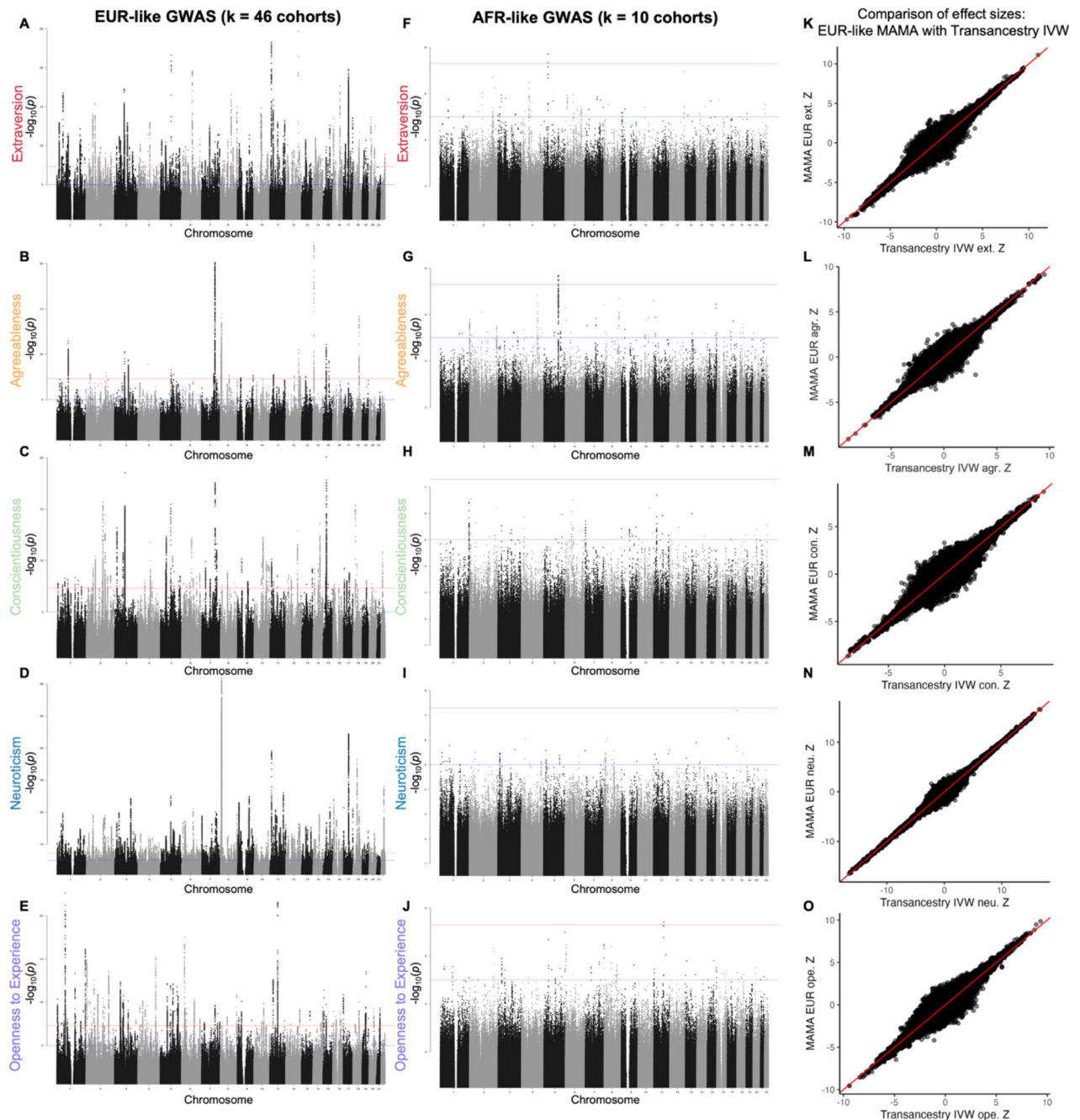
To enable direct comparison, we re-estimated population-level GWAS across these 12 within-family cohorts using the same method as in **Population-Level Association Meta-Analysis** above, restricted to SNPs with INFO $\geq .99$ and with sample size estimated using 1000 Genomes 3v5 panel MAF rather than meta-analytic sample MAF. We then submitted these within-family GWAS summary statistics and matched population GWAS summary statistics to LDSC.

To confirm that within-family analyses reduced confounding, we compared population-level LDSC intercepts to within-family LDSC intercepts³⁴. We employed nested model comparison tests in Genomic SEM to test the equivalence of h^2_{SNP} across matched population-level and within-family GWAS, and to test whether genetic correlations between

population-level and within-family GWAS were less than unity⁹⁵. We also compared the average SNP effect sizes between population-level and within-family GWAS, among SNPs with relatively strong statistical signal ($p < 1 \times 10^{-5}$) that were 250kb+ apart on the genome.

Using LDSC, we estimated genetic correlations between the Big Five within-family GWAS summary data and population-level GWAS summary data from the 85 external behaviors/outcomes. We compared these correlations to the corresponding estimates fully based on population-level GWAS. We also estimated genetic correlations fully based on within-family GWAS (for which summary data were available for 18 external behaviors/outcomes⁴ which compared to the corresponding estimates fully based on population-level GWAS.

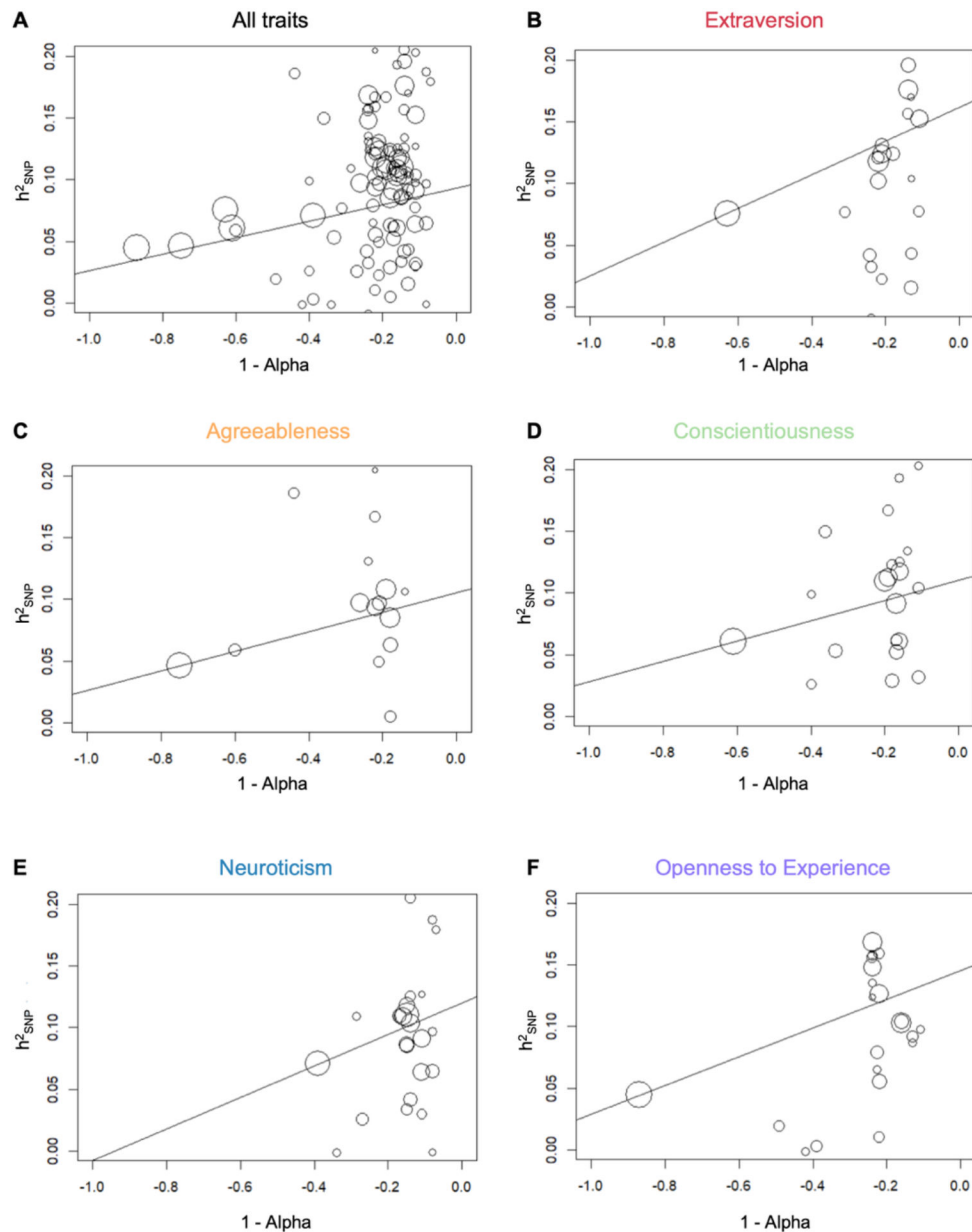
Extended Data



Extended Data Figure 1. Visualization of ancestry-specific meta-analyses.

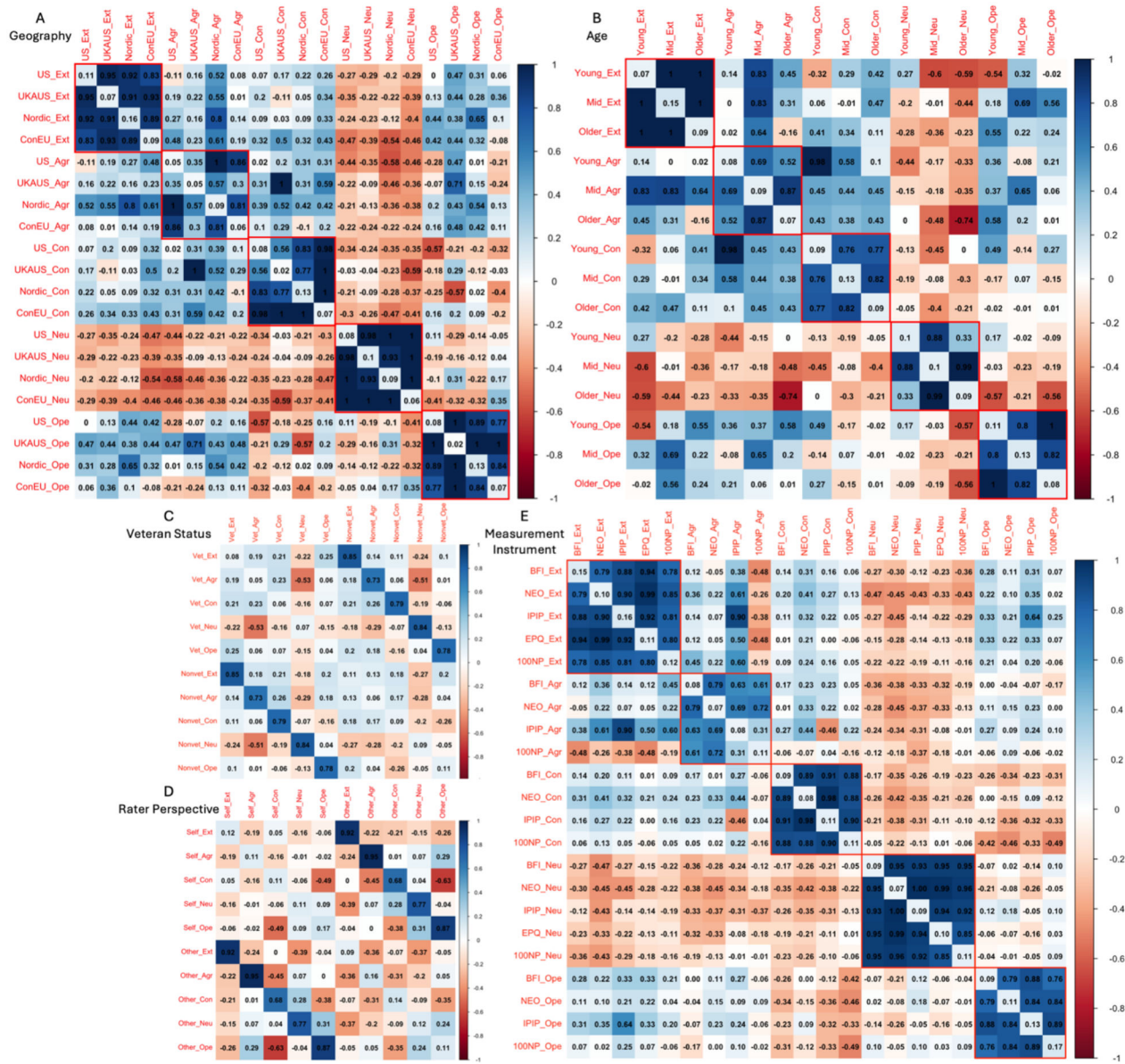
Panels A-E depict Manhattan plots among meta-analyzed cohorts of participants with EUR-like genomes for the traits of Extraversion (N = 620,193), agreeableness (N = 567,556), conscientiousness (N = 598,047), neuroticism (N = 1,088,604), and openness to experience (N = 568,489). See also Summary Table S4. Points correspond to two-sided test p-values of GWAS regressions. Genome wide significance is denoted with a red line, corrected for multiple comparisons at $p = 5 \times 10^{-8}$. P-values smaller than this threshold are considered

significant. The blue line indicates $p = 5 \times 10^{-5}$. **Panels F-J** depict Manhattan plots among meta-analyzed cohorts of participants with AFR-like genomes for the same traits: Extraversion (N = 43,201), agreeableness (N = 43,482), conscientiousness (N = 43,120), neuroticism (N = 48,110), and openness to experience (N = 43,498). See also Summary Table S4. **Panels K-O** depict similarity between (on the X axis) transancestry inverse-variance weighted meta-analytic GWAS Z-statistics and (on the Y axis) multi-ancestry meta-analysis GWAS Z-statistics for participants with EUR-like genomes boosted by data from participants with AFR-like genomes. Each dot represents a single SNP association with a Big Five trait, and the red line depicts an intercept of 0 and a slope of 1, visualizing the null hypothesis that effects are equivalent in magnitude between methods. See also Summary Table S17.



Extended Data Figure 2. Meta-regressions of SNP heritability against scale reliability across cohorts.

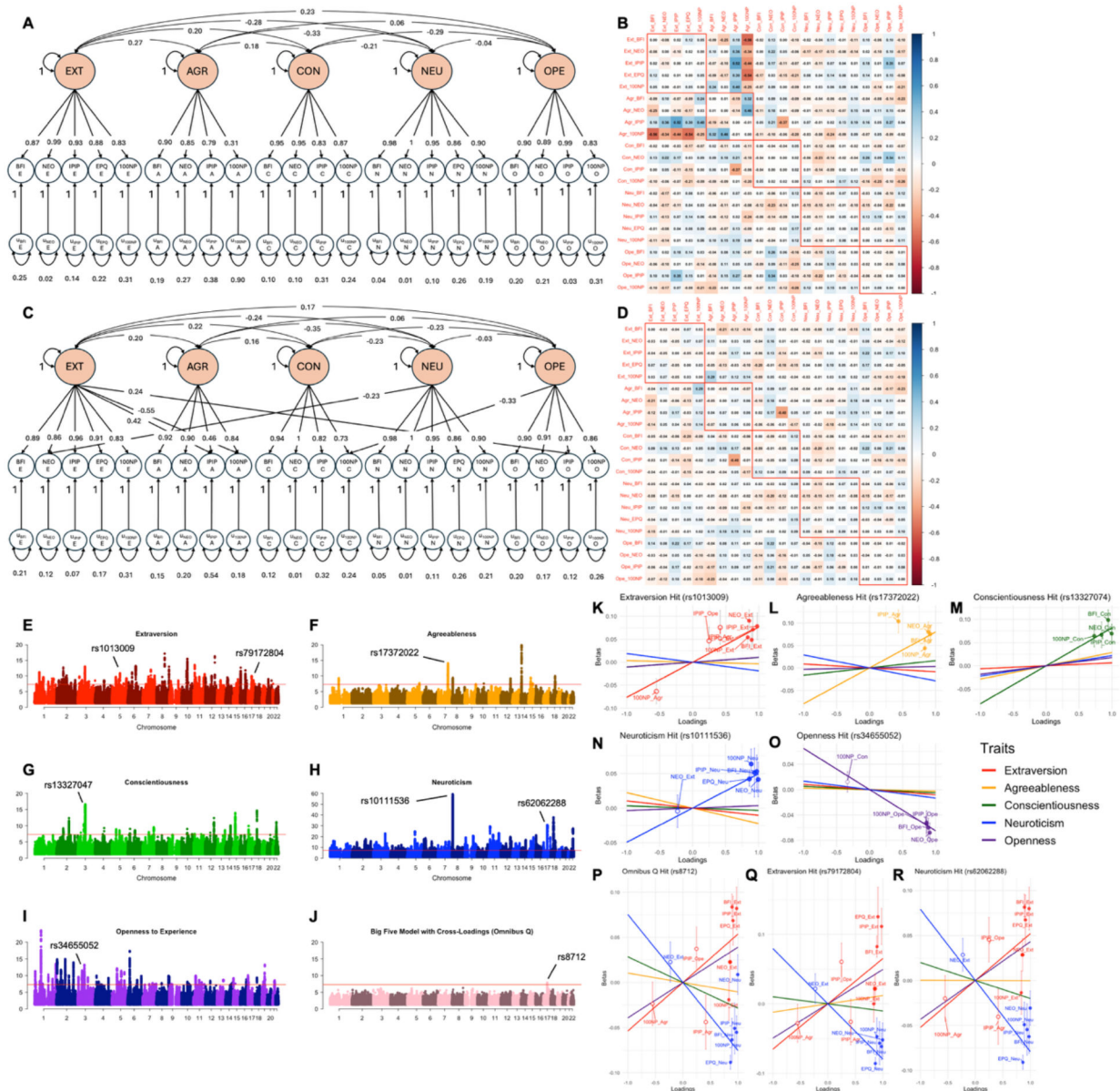
Note: The regression line depicts the association between scale reliability (Cronbach's Alpha) and h^2_{SNP} , weighted by inverse standard error of h^2_{SNP} estimate. Circles are scaled by inverse standard errors, such that larger circles represent more precise estimates. On the x-axis, Alpha values were re-scaled by subtracting 1 from all alpha values, such that an alpha of 0.0 represents perfect scale reliability. In **Panel A**, the regression is depicted for a multilevel model in which h^2_{SNP} is estimated for each trait, nested within each cohort. In **panels B-F**, the regression is depicted separately for each Big Five trait. See also Summary Tables S1 and S21.



Extended Data Figure 3. LDSC Genetic correlations stratified by groups: geographic regions, age groups, veteran status, rater perspective, and measurement instrument.

Panel A depicts associations between and among four geographic regions: US = United States. UKAUS = United Kingdom and Australia. ConEU = Continental Europe. Heritability of each trait in each group is presented on the diagonal. Red squares denote genetic correlations among measures of the same trait across groups. **Panel B** depicts correlations between and among young, medium, and old age groups. Young = Mean cohort age + $-1.5SD \leq 25$. Mid = Mean cohort age $\pm 1.5SD = 26-64$. Older = Mean cohort age $\pm 1.5SD \geq 65$. Heritability of each trait in each group is presented on the diagonal. Red squares denote genetic correlations among measures of the same trait across groups. **Panel C** depicts correlations between and among the Million Veterans Program sample, which is composed of US military veterans, and the other 45 ReGPC cohorts, which have few military veterans. Vet = Million Veterans Program. Nonvet = The Remaining 45 ReGPC cohorts. Heritability

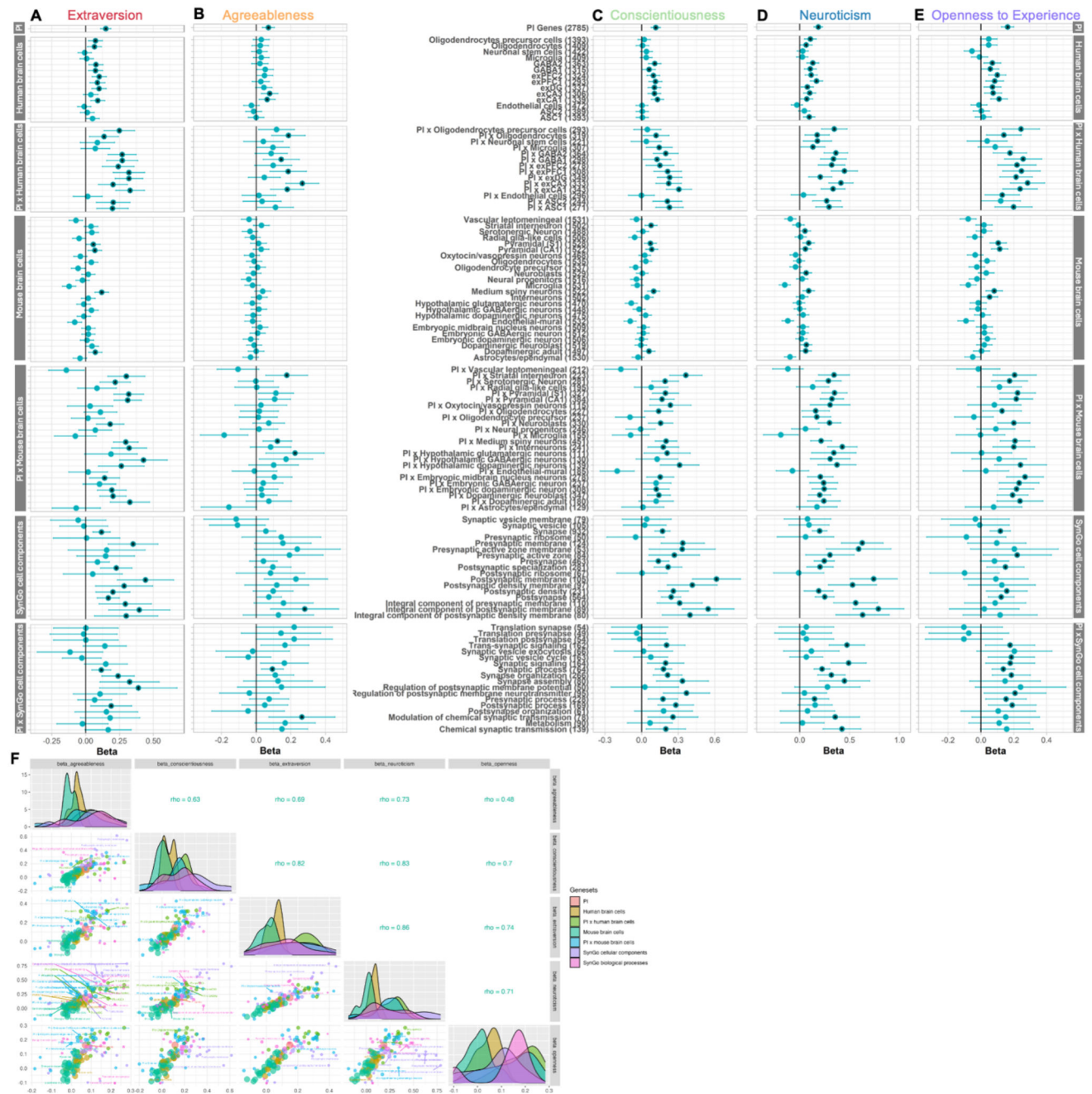
of each trait in each group is presented on the diagonal. **Panel D** depicts genetic correlations between and among self-rated and other-rated personality trait measurement in the Estonian Biobank. Heritability of each trait in each group is presented on the diagonal. **Panel E** depicts genetic correlations between and among personality measurement instruments. BFI = Big Five Inventory. NEO = NEO Inventory. IPIP = International Personality Item Pool. 100NP = 100 Nuances of Personality. EPQ = Eysenck Personality Questionnaire. Heritability of each questionnaire is presented on the diagonal. Red squares denote genetic correlations among measures of the same trait.



Extended Data Figure 4. Multivariate analysis of genetic signal across measurement instruments. **Panel A** depicts a confirmatory five-factor model of measurement-instrument stratified GWAS of the Big Five, conforming to simple structure. Standardized estimates are

displayed. BFI = Big Five Inventory. IPIP = International Personality Item Pool. NEO = NEO Inventory. EPQ = Eysenck Personality Questionnaire. 100NP = 100 Nuances of Personality. **Panel B** depicts the residual genetic correlation matrix for this confirmatory simple structure model. Red squares denote residual genetic correlations among measures of the same trait. To account for violations of simple structure, **Panel C** depicts the final factor model of measurement-instrument stratified GWAS of the Big Five, allowing for cross-loadings. **Panel D** depicts the residual genetic correlation matrix from this final factor model. **Panels E-I** depict Manhattan plots for each latent Big Five personality trait depicted in the Panel C measurement model and **panel J** depicts a Manhattan plot of Q_{SNP} from measurement-instrument stratified GWAS of the model in Panel C. In these panels, points correspond to two-sided test p -values of GWAS regressions. Genome wide significance is denoted with a red line, corrected for multiple comparisons at $p = 5 \times 10^{-8}$. P -values smaller than this threshold are considered significant. Note that the Y-axis scale for neuroticism is scaled differently than the other panels. See also Summary Table S23. **Panels K-O** plot SNP associations with each individual Big Five measure as a function of that measure's loading for a representative genome-wide significant hit with low Q_{SNP} for each trait. Each point depicts the relation between a SNP's association with an instrument (Beta) and the instrument's loading on the factor model in Panel C, with bars corresponding to the standard error of measurement. These SNPs are annotated in Panels E-I. The comparatively steep slope of the line corresponding to factor for which the SNP is a hit illustrates the specificity of the SNP effect on the factor, and the tight scatter of the points around their expectations is illustrative of the plausibility of assumption that the genetic variant operates on the individual measures via the factors (i.e. low Q_{SNP}). Both betas and factor loadings are standardized with respect to the genetic variance of the corresponding measure. Points are colored according to the trait on which the loading corresponds to. Solid points are primary loadings. Unfilled points are cross-loadings (from a measure of another trait). The superimposed lines have slopes equal to the estimated SNP effect on the respective trait, and represent the model-based expectations. N for each SNP are presented in Summary Table S24. **Panel P** plots SNP associations with different extraversion and neuroticism measures as a function of factor loading for a genome-wide-significant Q_{SNP} that is in high LD with Extraversion and Neuroticism hits (annotated in panel J). Each point depicts the relation between a SNP's association with an instrument (Beta) and the instrument's loading on the factor model in Panel C, with bars corresponding to the standard error of measurement. The diffuse scatter of the points around their expectations is illustrative of the implausibility of assumption that the genetic variant operates on the individual measures via the factors (i.e. high Q_{SNP}). Solid points are primary loadings. Unfilled points are cross-loadings (from a measure of another trait). The superimposed lines have slopes equal to the estimated SNP effect on the respective trait and represent the model-based expectations. N for each SNP are presented in Summary Table S24. **Panels Q and R** depict corresponding plots for extraversion and neuroticism hits (annotated in panels E and H, respectively). Each point depicts the relation between a SNP's association with an instrument (Beta) and the instrument's loading on the factor model in Panel C, with bars corresponding to the standard error of measurement. Both betas and loadings are standardized with respect to the genetic variance of the corresponding measure. Points are colored according to the trait on which the loading corresponds to. Solid points are primary loadings. Unfilled points are cross-loadings

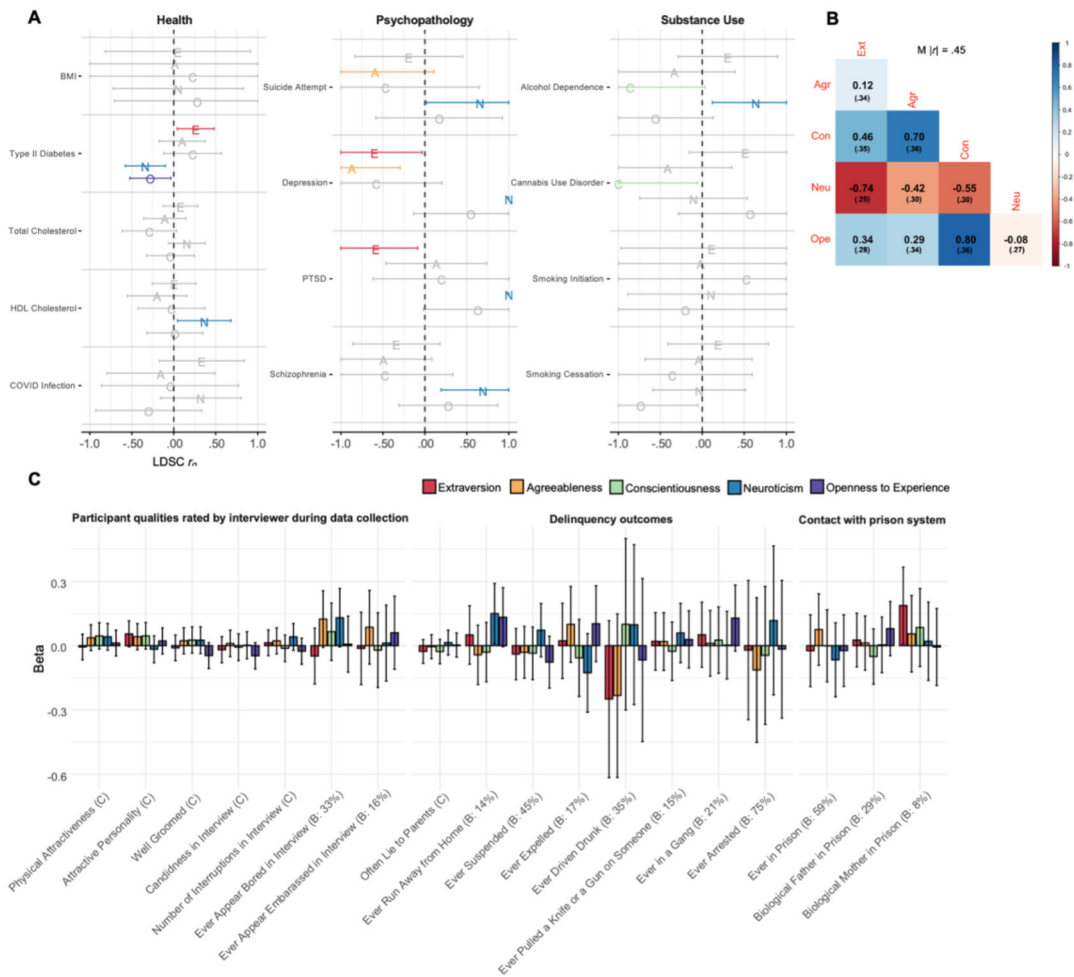
(from a measure of another trait). The superimposed lines have slopes equal to the estimated SNP effect on the respective trait and represent the model-based expectations.



Extended Data Figure 5. Gene-set heritability enrichment analyses.

Panels A-E depict enrichment for each of the Big Five traits. Each point estimate depicts the standardized enrichment beta; bars correspond to standard errors. PI = Protein-Truncating Intolerant genes. An X indicates the intersection of two gene sets. Number of genes in each set are in parentheses. Associations with a black star are significant after false-discovery-rate correction (Benjamini & Hochberg, 1995). **Panel F** depicts pairwise rank correlations of

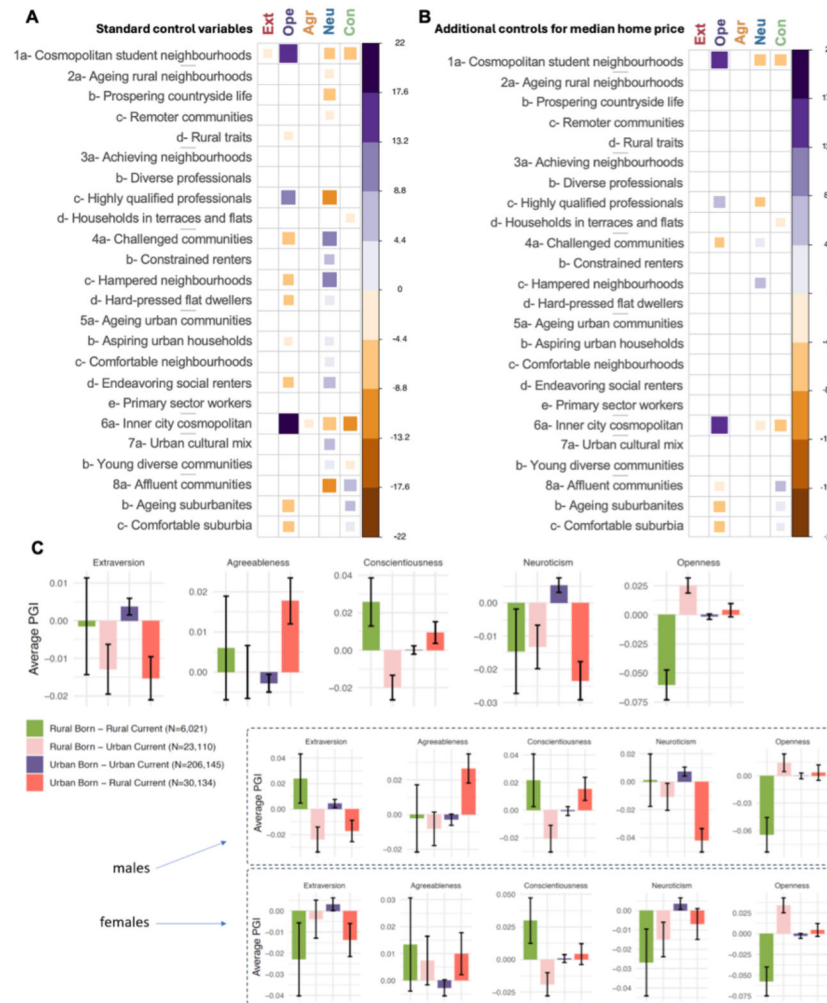
enrichment betas across the Big Five. Note: PI = Protein-truncating Intolerant genes. An X indicates the intersection of two gene sets. Larger points have larger weights, scaled by the inverse product of the standard errors of the gene set association betas. Gene sets with significantly differing enrichment across pairs of traits are labelled. See also Supplementary Tables S25–S29.



Extended Data Figure 6. Genetic correlations and PGI associations among participants with AFR-like genomes.

Panel A depicts Genetic correlations between personality and health, psychopathology, and substance use, estimated using LDSC. Letters correspond to point estimates of genetic correlation. Note: E = Extraversion. A = Agreeableness. C = Conscientiousness. N = Neuroticism. O = Openness to Experience. Error bars depict 99% confidence intervals. Associations not significant with two-sided test $p < .05$, with no further correction for multiple testing, are depicted in gray. Full numeric results are provided in Supplementary Table S38. **Panel B** depicts correlations among the Big Five in participants with AFR-like genomes. Note: Ext = Extraversion. Agr = Agreeableness. Con = Conscientiousness. Neu = Neuroticism. Ope = Openness to experience. Numbers in parentheses depict standard errors. Genetic correlations estimated using LDSC. **Panel C** depicts prediction of outcomes in the Add Health dataset from EUR-like GWAS personality trait polygenic indices applied

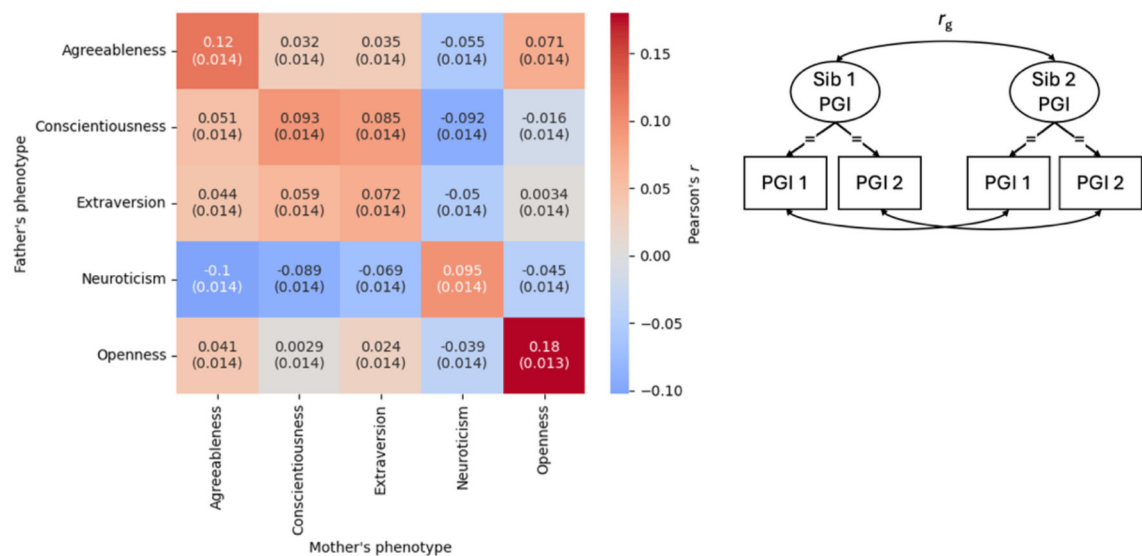
to participants with AFR-like genomes ($N = 1,753$). Note: Point estimates for effect sizes of continuous outcomes (labelled with a C) are in units of standardized beta, whereas associations with binary outcomes (labelled with a B, with percentage affirmative answers) are depicted in units of logistic beta. Error bars depict 95% confidence intervals. No associations are significant at two-sided test $p < .05$, with no further correction for multiple testing. Full numeric results are provided in Supplementary Table S39.



Extended Data Figure 7. Polygenic prediction of residential mobility.

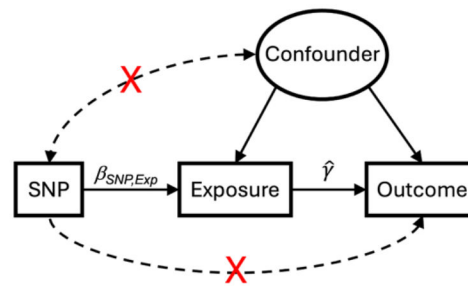
Panel A depicts a heatmap of residential preferences among UK Biobank participants with standard controls, based on the Z-statistics (right-hand bar) of the association between Big Five PGI and 22 area classifications. Associations are estimated controlling for 5 principal components, sex, age, genotyping array, and a fixed effect for MSOA region at birth. **Panel B** depicts a heatmap of residential preferences with additional controls for median home prices. This heatmap based on the Z-statistics (right-hand bar) of the association between Big Five PGI and 22 area classifications. Associations are estimated with controls in Panel A, plus additional control for local median home prices in 1995, 2000, 2005, and 2010. **Panel C** depicts PGI associations with moving or remaining in urban and rural areas

among participants in the UK Biobank, stratified by gender. Point estimates are in units of standardized beta. Error bars represent 95% confidence intervals.



Extended Data Figure 8. Assortative Mating.

Panel A depicts phenotypic correlations between mothers and fathers in the deCODE cohort (N = 5,317 unique mate pairs). Mates were defined as individuals known to have children together in the deCODE genealogical database. Each square shows the correlation coefficient with standard error in parenthesis. See also Supplementary Tables S40. **Panel B** depicts a structural equation model for estimating genetic assortative mating among partners. In the path diagram of the latent PGI model, the two PGIs estimated from split-half discovery GWAS data are depicted as PGI 1 and PGI 2. The factor loadings are constrained to be equal to one another, as denoted by an = sign, and the within-PGI cross-sibling PGI residual associations are allowed to correlate. Factor variances are constrained to 1 to identify the metric of the genetic factors.

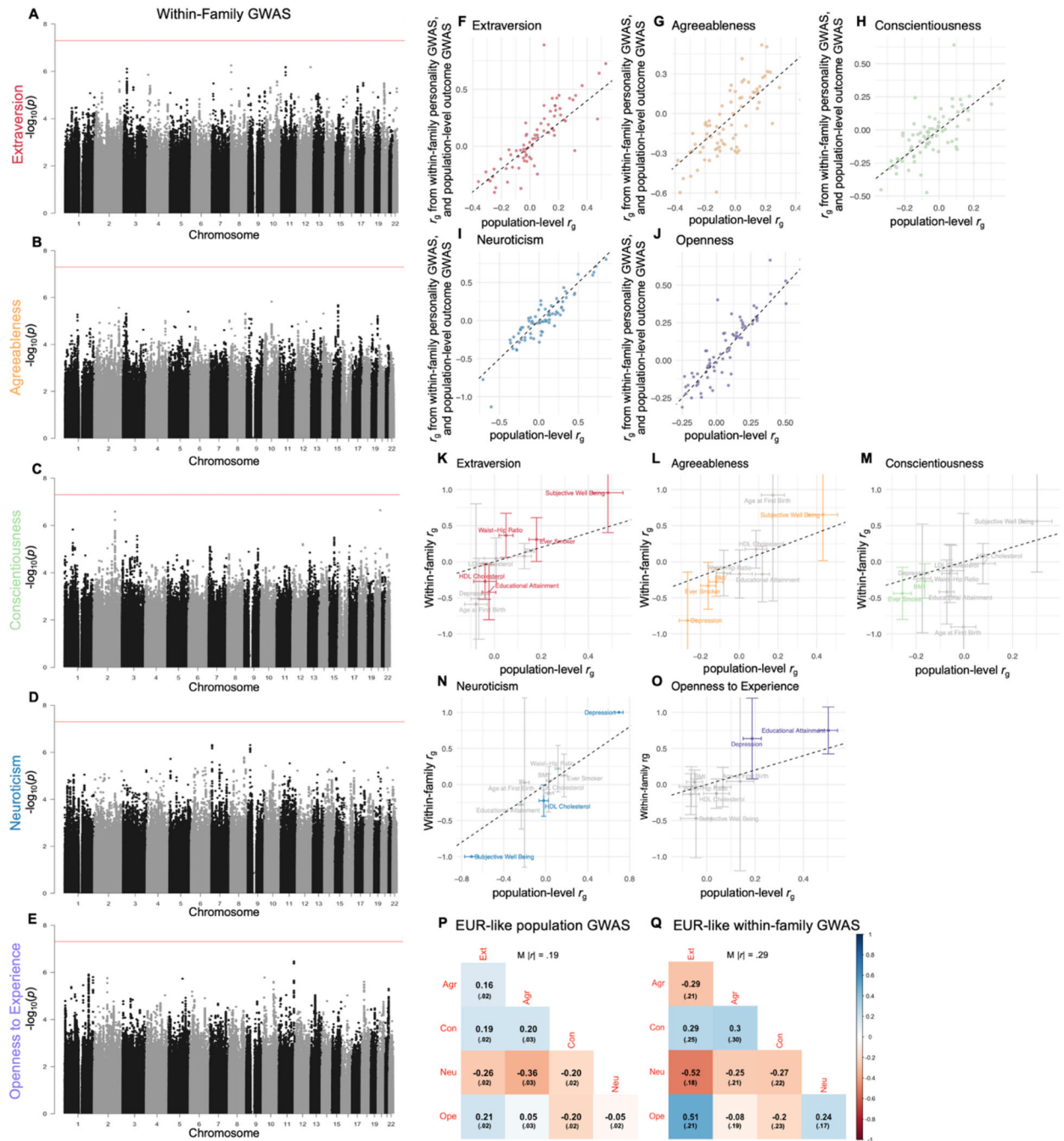


Mendelian Randomization Estimator				
Exposure	Outcome	Weighted median	MR-CAUSE	Weighted mode
Personality -> Outcome	Extraversion			
	Age at first sex	-.15 (-.09, -.20)	-.06 (-.10, -.02)	-.15 (-.04, -.27)
	COVID infection	.16 (.09, .24)	.09 (.04, .13)	.15 (-.07, .36)
	Drinks per week	.11 (.08, .14)	.07 (.05, .10)	.06 (-.07, .18)
	Spells in hospital	-.09 (-.14, -.05)	-.09 (-.12, -.07)	-.11 (-.30, .07)
	Study part.: "I don't know"	-.04 (-.06, -.01)	-.04 (-.06, .02)	-.05 (-.13, .04)
	Agreeableness			
	Age at first sex	.21 (.03, .39)	.11 (.04, .17)	.31 (.00, .62)
	Educational attainment	.20 (.10, .30)	.11 (.05, .18)	.32 (.15, .49)
	Sports Frequency	-.57 (-.97, -.17)	-.03 (-.17, .12)	-.67 (-1.15, -.20)
	Conscientiousness			
	Body Mass Index	-.14 (-.22, -.06)	-.14 (-.19, -.08)	-.10 (-.26, .06)
	Educational attainment	-.07 (-.13, -.01)	-.02 (-.05, -.01)	-.12 (-.23, -.00)
	Smoking initiation	-.18 (-.24, -.13)	-.10 (-.13, -.06)	-.18 (-.28, -.07)
	Spells in hospital	-.12 (-.19, -.06)	-.06 (-.09, -.04)	-.19 (-.38, -.00)
	Neuroticism			
	Body Mass Index	.04 (.01, .07)	.03 (-.01, .07)	.19 (.06, .32)
	Longevity	-.08 (-.09, -.07)	-.08 (-.10, -.07)	-.08 (-.17, .00)
	Smoking initiation	.05 (.03, .08)	.11 (.08, .13)	.15 (-.00, .30)
	Spells in hospital	.09 (.05, .12)	.05 (.03, .07)	.10 (.01, .19)
	Study part.: Diet optional questionnaire	-.05 (-.06, -.04)	-.04 (-.05, -.03)	-.06 (-.11, -.01)
	Study part.: Mental Health optional questionnaire	-.04 (-.06, -.03)	-.06 (-.07, -.05)	-.03 (-.09, .04)
	Study part.: Physical activity optional questionnaire	-.08 (-.12, -.05)	-.10 (-.13, -.07)	-.08 (-.21, .06)
	Study part.: "I don't know"	.06 (.04, .08)	.08 (.06, .10)	.02 (-.07, .11)
	Openness			
	Educational attainment	.26 (.30, .33)	.29 (.24, .33)	.15 (-.02, .33)
	Study part.: Diet optional questionnaire	.04 (.02, .06)	.03 (.02, .05)	.02 (-.03, .07)
	Study part.: Mental Health optional questionnaire	.04 (.02, .06)	.04 (.03, .05)	.02 (-.05, .10)
	Study part.: "I don't know"	-.05 (-.09, -.02)	-.05 (-.07, -.02)	-.05 (-.14, .05)
Outcome -> Personality	Body Mass Index			
	Agreeableness	-.04 (-.05, -.02)	-.04 (-.06, -.02)	-.06 (-.12, -.00)
	Conscientiousness	-.06 (-.07, -.04)	-.05 (-.08, -.02)	-.05 (-.11, -.00)
	Edu. attainment			
	Agreeableness	.05 (.03, .07)	.05 (.03, .07)	.05 (-.07, .16)
	Neuroticism	-.13 (-.15, -.12)	-.11 (-.13, -.10)	-.20 (-.28, -.12)
	Openness	.23 (.21, .26)	.20 (.18, .22)	.29 (.20, .38)
	Smoking initiation			
	Extraversion	.11 (.07, .14)	.09 (.06, .12)	.13 (-.01, .28)
	Agreeableness	-.06 (-.10, -.03)	-.08 (-.10, -.05)	-.10 (-.14, -.07)
	Conscientiousness	-.10 (-.14, -.07)	-.09 (-.13, -.06)	-.14 (-.27, -.00)
	Neuroticism	.04 (.01, .06)	.08 (-.05, .11)	.02 (-.08, .12)

Extended Data Figure 9. Mendelian Randomization.

Panel A depicts the causal diagram assumed by Mendelian Randomization (MR) approaches. The dashed lines with the red X represent paths assumed to be absent by traditional MR. The three approaches to MR that were implemented in this paper use different approaches to estimating causal effects of the exposure on the outcome using multiple independent SNPs, such that they are robust to violations of these standard assumptions by a subset of SNPs. These approaches are described in the Supplementary Text. **Panel B** depicts results of MR tests that indicate putatively causal effects of personality

traits on outcomes, or of outcomes on personality traits. Effects are bolded if the 95% confidence interval (in parentheses) excludes zero. For each pairing of exposure and outcome, we consider effects significant if confidence intervals exclude zero for at least two of the three estimators. Note: MR-CAUSE = Mendelian Randomization Causal Analysis Using Summary Effect estimates. Study Part.: = Study participation. IDK = “I don’t know” response. Summary statistics for outcomes are described in Supplementary Table S37. Numbers in parentheses indicate 95% confidence intervals (for weighted median and weighted mode tests) or 95% credible intervals (for MR-CAUSE tests). Bolded numbers indicate 95% confidence/credible interval excludes 0. Results presented here only include exposure-outcome pairs where the 95% credible interval/confidence interval for at least 2 out of 3 tests excludes zero, and all three tests produce estimates in the same direction. See also Supplementary Tables S42–S43.



Extended Data Figure 10. Within-Family GWAS results.

Panels A-E depict Manhattan plots among meta-analyzed cohorts of participants with EUR-like genomes for the traits of Extraversion ($N = 47,630$), agreeableness ($N = 31,607$), conscientiousness ($N = 31,544$), neuroticism ($N = 55,637$), and openness to experience ($N = 32,216$). In these panels, points correspond to two-sided test p -values of GWAS regressions. Genome wide significance is denoted with a red line, corrected for multiple comparisons at $p = 5 \times 10^{-8}$. P -values smaller than this threshold are considered significant. The blue line indicates $p = 5 \times 10^{-5}$. See also Supplementary Table S47. **Panels F-J** depict

the correspondence between (on the X axis) population-level genetic correlations between personality traits and external outcomes (from Figure 3 in the main text) and (on the Y axis) genetic correlations where personality trait data come from within-family GWAS and external outcome data come from population-level GWAS. Each of 85 personality-outcome correlations are plotted for each of the Big Five. The dashed line with a slope of 1 and an intercept of 0 depicts equality in correlations across the two estimates. Genetic correlations were estimated using LDSC. See also Supplementary Table S48. **Panels K-O** depict the correspondence between (on the X axis) population-level genetic correlations between personality traits and external outcomes, using population-level GWAS data (from Figure 3 in the main text) and (on the Y axis) within-family genetic correlations between personality traits and external outcomes, using within-family GWAS data. Within-family GWAS data of external outcomes come from Howe and colleagues (2022). For each outcome, 95% confidence intervals are presented stretching horizontally, for inferential uncertainty in population-level estimates, and vertically, for inferential uncertainty in within-family estimates. Outcomes are colored if the within-family genetic correlation is significant at $p < .05$ and gray if nonsignificant. The dashed line with a slope of 1 and an intercept of 0 depicts equality in correlations across the two estimates. Genetic correlations were estimated using LDSC. See also Supplementary Table S49. **Panel P** depicts LDSC genetic correlations across the Big Five for the full population-level meta-analytic sample, and **Panel Q** depicts LDSC genetic correlations across the Big Five for the within-family meta-analytic sample. Numbers in parentheses represent standard errors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Ted Schwaba^{1,*}, Margaret L. Clapp Sullivan², Wonuola A. Akingbuwa^{3,4}, Kerli Ilves⁵, Peter T. Tanksley⁶, Camille M. Williams⁷, Yavor Dragostinov^{2,8}, Travis T. Mallard^{9,10,11,12}, Justin D. Tubbs^{9,10,11,12}, Wangjingyi Liao¹³, Lindsay S. Ackerman¹, Josephine C. M. Fealy¹, Gibran Hemani^{14,15}, Javier de la Fuente², George Davey Smith^{14,15}, Priya Gupta¹⁶, Murray B. Stein¹⁷, Joel Gelernter¹⁶, Daniel F. Levey¹⁶, Urmo Vösa⁵, Liisi Ausmees¹⁸, Anu Realo^{18,19,20}, Estonian Biobank Research Team^{**}, Mariliis Vaht⁵, Jüri Allik¹⁹, Tõnu Esko⁵, René Mõttus^{18,21}, Uku Vainik^{5,19,22}, Gudrun A. Jonsdottir²³, Gudmar Thorleifsson²³, Árni Freyr Gunnarsson²³, Gyda Bjornsdottir²³, Thorgerir E. Thorgerirsson²³, Hreinn Stefansson²³, Kari Stefansson²³, Rosa Cheesman^{24,25}, Qi Qin²⁴, Elizabeth C. Corfield^{14,26,27}, Helga Ask^{24,26}, Fartein Ask Torvik^{24,28}, Eivind Ystrom^{24,26,29}, Martin Tesli^{30,31}, Dorret I. Boomsma³², Eco J. C. de Geus^{3,4}, Jouke-Jan Hottenga³, Dener Cardoso Melo³³, Harold Snieder³⁴, Catharina A. Hartman^{21,33}, Charley Xia^{21,35}, Archie Campbell³⁶, Michelle Luciano²¹, Ian J. Deary^{21,3}, W. David Hill^{21,35}, Seon-Kyeong Jang³⁷, Scott I. Vrieze^{38,39}, Gonçalo Abecasis⁴⁰, Michelle K. Lupton^{41,42,43}, Brittany L Mitchell^{41,42,43}, Petra V. Viher⁴¹, Lucía Colodro-Conde^{41,44}, Nicholas G. Martin⁴¹, Sarah E. Medland^{41,44}, Eske M. Derks⁴¹, Briar Wormington⁴¹, Jaakko Kaprio⁴⁵,

Karri Silventoinen⁴⁶, Teemu Palviainen⁴⁵, Agnieszka Musial¹³, Kaili Rimfeld^{47,48}, Robert Plomin⁴⁸, Margherita Malanchini¹³, Danielle M. Dick^{49,50}, Fazil Aliev⁵⁰, COGA Collaborators^{**}, The Spit for Science Working Group^{**}, Laura W. Wesseldijk^{51,52,53}, Fredrik Ullén^{51,52}, Miriam A. Mosing^{52,54,55}, Henry R. Kranzler⁵⁶, Yaira Nunez⁵⁷, Sarah Beck⁵⁷, Renato Polimanti⁵⁷, Tobias Edwards³⁸, Alexandros Giannelis³⁸, Emily A. Willoughby³⁸, James J. Lee³⁸, Matt McGue³⁸, Antonio Terracciano^{58,59}, Michele Marongiu⁶⁰, Edoardo Fiorillo⁶⁰, Francesco Cucca⁶¹, Angelina R. Sutin⁶², Peter J. van der Most³⁴, Albertine J. Oldehinkel³³, Tina Kretschmer⁶³, Andrey A. Shabalin⁶⁴, Anna R. Docherty⁶⁵, Robert F. Krueger³⁸, Colin D. Freilich³⁸, Binisha H. Mishra^{65,66,67}, Terho Lehtimäki^{65,66,67}, Olli T. Raitakari^{68,69,70,71}, Mika Kähönen^{66,72}, Aino Saarinen⁷³, Henrik Dobewall⁷⁴, Liisa Keltikangas-Järvinen⁷³, Klaus Berger⁷⁵, Marisol Herrera-Rivero^{75,76}, Fabian Streit^{77,78,79}, Swapnil Awasthi⁸⁰, Stephanie H. Witt⁸¹, Johanna Tuhkanen⁸², Katri Räikkönen⁸³, Johan G. Eriksson^{83,84,85}, Jari Lahti^{82,84}, Gail Davies³⁵, Paul Redmond³⁵, Adele Taylor³⁵, Janie Corley³⁵, Tom C. Russ^{86,87}, Marina Ciullo⁸⁸, Teresa Nutile⁸⁸, Jun Ding⁸⁹, Yong Qian⁸⁹, Toshiko Tanaka⁸⁹, Luigi Ferrucci⁸⁹, Lea Zillich⁸¹, Lea Sirignano⁸¹, K. Paige Harden², Erhan Genç⁹⁰, Patrick D. Gajewski⁹¹, Stephan Getzmann⁹¹, Christoph Fraenz⁹⁰, Javier E. Schneider Peñate⁹², Stefanie Lis^{93,94}, Alisha S. M. Hall^{81,95,96}, Christian Schmahl⁹³, Sabine C. Herpertz⁹⁷, Abdel Abdellaoui^{53,98}, Michel G. Nivard^{14,15,*†}, Elliot M. Tucker-Drob^{2,8,*†}

Affiliations

- ¹Department of Psychology, Michigan State University, East Lansing, MI, USA
- ²Department of Psychology, University of Texas at Austin, Austin, TX, USA
- ³Department of Biological Psychology, Faculty of Behavioural and Movement Sciences, Vrije Universiteit, Amsterdam, the Netherlands.
- ⁴Amsterdam Public Health Research Institute, Amsterdam University Medical Centre, Amsterdam, the Netherlands.
- ⁵Institute of Genomics, University of Tartu, Estonia
- ⁶ALERRT Center, Texas State University
- ⁷Laboratoire de Sciences Cognitives et Psycholinguistique (ENS, EHESS, CNRS), École Normale Supérieure, PSL University, Paris, France
- ⁸Population Research Center, University of Texas at Austin, Austin, TX, USA
- ⁹Center for Precision Psychiatry, Department of Psychiatry, Massachusetts General Hospital, Boston, MA
- ¹⁰Psychiatric and Neurodevelopmental Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA
- ¹¹Department of Psychiatry, Harvard Medical School, Boston, MA

- ¹²Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA
- ¹³School of Biological and Behavioral Sciences, Queen Mary University of London, London, UK
- ¹⁴Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK
- ¹⁵Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
- ¹⁶Yale University, Veterans Affairs Connecticut Healthcare System
- ¹⁷University of California San Diego, Veterans Affairs San Diego Healthcare System
- ¹⁸Institute of Psychology, University of Tartu, Estonia
- ¹⁹Department of Psychology, University of Warwick, UK
- ²⁰School of Educational Sciences, Tallinn University, Estonia
- ²¹Department of Psychology, University of Edinburgh, Edinburgh, UK
- ²²Montreal Neurological Institute, McGill University, Canada
- ²³deCODE genetics/Amgen, Reykjavik, Iceland
- ²⁴PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway
- ²⁵School of Psychology and Neuroscience, University of Bristol, Bristol, UK
- ²⁶PsychGen Centre for Genetic Epidemiology and Mental Health, Division of Public Health and Prevention, Norwegian Institute of Public Health, Oslo, Norway
- ²⁷Psychiatric Genetic Epidemiology Group, Research Department, Lovisenberg Diaconal Hospital, Oslo, Norway
- ²⁸Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway
- ²⁹Centre for Research on Equality in Education, Faculty of Educational Sciences, University of Oslo, Oslo, Norway
- ³⁰Department of Mental Health, Norwegian Institute of Public Health, Oslo, Norway
- ³¹Department of Psychiatry, Østfold Hospital, Norway
- ³²Department of Complex Trait Genetics, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands
- ³³Interdisciplinary Center Psychopathology and Emotion Regulation (ICPE), University of Groningen, University Medical Center Groningen, Groningen, The Netherlands
- ³⁴Epidemiology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

- ³⁵.Lothian Birth Cohort Studies, Department of Psychology, University of Edinburgh, Edinburgh, UK
- ³⁶.Centre for Genomic and Experimental Medicine, Institute of Genetics and Cancer, University of Edinburgh, Edinburgh, UK
- ³⁷.Department of Computational Medicine, University of California Los Angeles, Los Angeles
- ³⁸.Department of Psychology, University of Minnesota
- ³⁹.Minnesota Center for Twin and Family Research
- ⁴⁰.Regeneron Genetics Center, Regeneron Pharmaceuticals
- ⁴¹.QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia
- ⁴².Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia
- ⁴³.School of Biomedical Sciences, Queensland University of Technology, Brisbane, QLD, Australia.
- ⁴⁴.School of Psychology, The University of Queensland, Brisbane, QLD, Australia
- ⁴⁵.Institute for Molecular Medicine FIMM, University of Helsinki, Helsinki, Finland
- ⁴⁶.Population Research Unit, Faculty of Social Sciences, University of Helsinki, Helsinki, Finland
- ⁴⁷.Department of Psychology, Royal Holloway University of London, Egham, UK
- ⁴⁸.Social, Genetic, & Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
- ⁴⁹.Rutgers Addiction Research Center, Brain Health Institute, Rutgers University
- ⁵⁰.Department of Psychiatry, Rutgers Robert Wood Johnson Medical School
- ⁵¹.Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden
- ⁵².Department of Cognitive Neuropsychology, Max Planck Institute for Empirical Aesthetics, Frankfurt am Main, Germany
- ⁵³.Department of Psychiatry, Amsterdam University Medical Centre, University of Amsterdam
- ⁵⁴.Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
- ⁵⁵.Melbourne School of Psychological Sciences, University of Melbourne, Australia
- ⁵⁶.Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States
- ⁵⁷.Department of Psychiatry, Yale School of Medicine, New Haven CT, United States
- ⁵⁸.Department of Geriatrics, College of Medicine, Florida State University, Tallahassee
- ⁵⁹.Laboratory of Behavioral Neuroscience, National Institute on Aging, Baltimore

- ⁶⁰.Institute for Genetic and Biomedical Research, Consiglio Nazionale delle Ricerche (CNR), Cagliari, Italy
- ⁶¹.Department of Biomedical Sciences, University Study of Sassari, Sassari, Italy
- ⁶².Department of Behavioral Sciences and Social Medicine, College of Medicine, Florida State University, Tallahassee
- ⁶³.Pedagogical Sciences, Faculty of Behavioural and Social Sciences, University of Groningen, Groningen, The Netherlands
- ⁶⁴.Huntsman Mental Health Institute, Department of Psychiatry, University of Utah
- ⁶⁵.Department of Clinical Chemistry, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
- ⁶⁶.Finnish Cardiovascular Research Center Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland
- ⁶⁷.Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland
- ⁶⁸.Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland
- ⁶⁹.Centre for Population Health Research, University of Turku and Turku University Hospital, Turku, Finland
- ⁷⁰.Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku, Turku, Finland
- ⁷¹.InFLAMES Research Flagship, University of Turku, Turku, Finland
- ⁷².Department of Clinical Physiology, Tampere University Hospital, Tampere Finland
- ⁷³.Faculty of Medicine, Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland
- ⁷⁴.Finnish Institute for Health and Welfare
- ⁷⁵.Institute of Epidemiology and Social Medicine, University of Münster, Germany
- ⁷⁶.Department of Genetic Epidemiology, Institute of Human Genetics, Germany
- ⁷⁷.Hector Institute for Artificial Intelligence in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
- ⁷⁸.Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
- ⁷⁹.German Center for Mental Health (DZPG), Partner Site Mannheim - Heidelberg - Ulm, Germany
- ⁸⁰.Department of Psychiatry and Psychotherapy, Campus Mitte Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany
- ⁸¹.Department of Genetic Epidemiology in Psychiatry, Medical Faculty Mannheim/ Heidelberg University, Central Institute of Mental Health, Mannheim, Germany

- ⁸².Department of Psychology, University of Helsinki, Helsinki, Finland
- ⁸³.Department of General Practice and Primary Health Care, Tukholmankatu 8 B, University of Helsinki, Finland
- ⁸⁴.Folkhälsan Research Centre, Helsinki, Finland
- ⁸⁵.National University Singapore, Yong Loo Lin School of Medicine, Department of Obstetrics and Gynecology, Singapore, Singapore
- ⁸⁶.Alzheimer Scotland Dementia Research Centre, University of Edinburgh, United Kingdom
- ⁸⁷.Division of Psychiatry, Centre for Clinical Brain Sciences, University of Edinburgh, United Kingdom
- ⁸⁸.Institute of Genetics and Biophysics “Adriano Buzzati-Traverso” - CNR, Naples, Italy
- ⁸⁹.Translational Gerontology Branch, National Institute on Aging, Baltimore
- ⁹⁰.Department of Psychology and Neurosciences, Neuroimaging and Interindividual Differences, Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany
- ⁹¹.Department of Ergonomics, Networking Group Aging, Leibniz Research Centre for Working Environment and Human Factors (IfADo), Dortmund, Germany
- ⁹².Department of Psychology, Neuropsychology, Ruhr University Bochum, Bochum, Germany
- ⁹³.Department of Psychosomatic Medicine and Psychotherapy, Medical Faculty Mannheim/Heidelberg University, Central Institute of Mental Health, Mannheim, Germany
- ⁹⁴.Department of Clinical Psychology, Medical Faculty Mannheim/Heidelberg University, Central Institute of Mental Health, Mannheim, Germany
- ⁹⁵.Department of Affective Disorders, Aarhus University Hospital, Aarhus, Denmark
- ⁹⁶.Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
- ⁹⁷.Department of Psychosomatic General Psychiatry, Center for Psychosocial Medicine, Medical Faculty Mannheim/Heidelberg University, Heidelberg, Germany
- ⁹⁸.Amsterdam Neuroscience, Amsterdam, The Netherlands

Acknowledgements

Acknowledgements for individual cohorts can be found in Supplementary Note 7.

Funding

T.S., W.A.A., M.G.N., M.L.C.S., C.M.W., and E.M.T-D. were supported by NIMH R01MH120219. E.M.T-D., M.L.C.S., C.M.W., Y.D. and J.F. were supported by NIA R01AG073593. W.A.A. is also supported by a Dutch Ministry of Education, Culture, and Sciences (OCW) Talent and Early Development Grant. MGN, ECC, GH, and GDS are members of the MRC Integrative Epidemiology Unit at the University of Bristol which is supported

by the Medical Research Council and the University of Bristol (MC_UU_00032/1 & MC_UU_00032/7). J.D.T. was supported by NIMH K01MH141330. W.D.H., and C.X. were supported by a Career Development Award from the Medical Research Council (MRC) [MR/T030852/1] for the project titled “From genetic sequence to phenotypic consequence: genetic and environmental links between cognitive ability, socioeconomic position, and health.” T.K. was funded by the European Research Council (ERC Consolidator Grant awarded under the Horizon Europe framework, grant agreement 101087395. F.S. was supported by the Hector foundation II and by a 2023 NARSAD Young Investigator Grant (#31537) from the Brain & Behavior Research Foundation with support from the Families for Borderline Personality Disorder Research. R.C. was supported by the Jacobs Foundation grant no. 2023-1510-00 and the Research Council of Norway (grant number 325245). H.A. was supported by the research council of Norway (#274611, #324620). F.A.T. was supported by Research Council of Norway #262700. E.C.C. was supported by the research council of Norway (RCN; #274611) and the South-Eastern Norway Regional Health Authority (HSØ; #2021045). J.L. received financial support from the Strategic Research Council (SRC) established within the Academy of Finland (decision number: 352700). K.I. and U.Vainik have been funded by Estonian Research Council’s personal research funding start-up grants PSG656 and PSG759. R.M. has been funded by Estonian Research Council’s team grant PRG2190. U.Võsa and T.E. have been funded by Estonian Research Council’s team grant PRG1291. A.A. is supported by the Amsterdam UMC Fellowship. T.T. and L.F. were supported in part by the National Institute on Aging Intramural Research Program. A.G. was supported by the European Research Council (GEPSI 946647). Acknowledgments for cohort funding are included in the Supplementary Text.

Data Availability

Summary statistics for GWAS of each Big Five trait, excluding 23andMe participants, are available at <https://doi.org/10.17605/OSF.IO/HGNSM>. This includes EUR-like, AFR-like, and trans-ancestry meta-analytic population-level summary statistics, polygenic index weights, and EUR-like within-family summary statistics, neuroticism summary statistics both including and excluding UK Biobank participants, and country-, age-, perspective- and questionnaire-stratified summary statistics. Other data used in this study cannot be made public and are available, within the constraints of the relevant regulations and data use agreements, upon request.

Code Availability

Code for all analyses performed this study is available at <https://doi.org/10.17605/OSF.IO/HGNSM>

Main references

1. Roberts BW, & Yoon HJ. (2022). Personality psychology. *Annual review of psychology*, 73(1), 489–516.
2. McCrae RR, & John OP. (1992). An introduction to the five-factor model and its applications. *Journal of personality*, 60(2), 175–215.
3. Gupta P, Galimberti M, Liu Y, Beck S, Wingo A, Wingo T, ... & Levey DF. (2024). A genome-wide investigation into the underlying genetic architecture of personality traits and overlap with psychopathology. *Nature human behaviour*, 8, 2235–2249.
4. Howe LJ, Nivard MG, Morris TT, Hansen AF, Rasheed H, Cho Y, ... & Davies NM. (2022). Within-sibship genome-wide association analyses decrease bias in estimates of direct genetic effects. *Nature genetics*, 54(5), 581–592.
5. Tan T, Jayashankar H, Guan J, Nehzati SM, Mir M, Bennett M, ... & Young AS. (2024). Family-GWAS reveals effects of environment and mating on genetic associations. *medRxiv*, 2024-10.
6. John OP, Naumann LP, & Soto CJ. (2008). Paradigm shift to the integrative big five trait taxonomy. *Handbook of Personality: Theory and Research*, 3(2), 114–158.
7. Matthews G, Deary IJ, & Whiteman MC. (2009). *Personality traits*. Cambridge University Press.
8. Anni K, Vainik U, & Möttus R. (2024). Personality profiles of 263 occupations. *Journal of Applied psychology*.

9. Borghans L, Golsteyn BH, Heckman JJ, & Humphries JE. (2016). What grades and achievement tests measure. *Proceedings of the National Academy of Sciences*, 113(47), 13354–13359.
10. Roberts BW, Kuncel NR, Shiner R, Caspi A, & Goldberg LR. (2007). The power of personality: The comparative validity of personality traits, socioeconomic status, and cognitive ability for predicting important life outcomes. *Perspectives on psychological science*, 2(4), 313–345.
11. Hampson SE, Goldberg LR, Vogt TM, & Dubanoski JP. (2007). Mechanisms by which childhood personality traits influence adult health status: educational attainment and healthy behaviors. *Health psychology*, 26(1), 121–125.
12. Moffitt TE, Arseneault L, Belsky D, Dickson N, Hancox RJ, Harrington H, ... & Caspi A. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, 108(7), 2693–2698.
13. Kotov R, Gamez W, Schmidt F, & Watson D. (2010). Linking “big” personality traits to anxiety, depressive, and substance use disorders: a meta-analysis. *Psychological bulletin*, 136(5), 768–821.
14. Widiger TA, Sellbom M, Chmielewski M, Clark LA, DeYoung CG, Kotov R, ... & Wright AG. (2019). Personality in a hierarchical model of psychopathology. *Clinical psychological science*, 7(1), 77–92.
15. Antonoplis S, & John OP. (2022). Who has different-race friends, and does it depend on context? Openness (to other), but not agreeableness, predicts lower racial homophily in friendship networks. *Journal of personality and social psychology*, 122(5), 894–919.
16. Jokela M. (2020). Selective residential mobility and social influence in the emergence of neighborhood personality differences: Longitudinal data from Australia. *Journal of research in personality*, 86, 103953.
17. Duckitt J, & Sibley CG. (2010). Personality, ideology, prejudice, and politics: A dual-process motivational model. *Journal of personality*, 78(6), 1861–1894.
18. Sanchez-Roige S, Jennings MV, Thorpe HH, Mallari JE, van der Werf LC, Bianchi SB, ... & Palmer AA. (2023). CADM2 is implicated in impulsive personality and numerous other traits by genome-and phenome-wide association studies in humans and mice. *Translational Psychiatry*, 13(1), 167.
19. Lo MT, Hinds DA, Tung JY, Franz C, Fan CC, Wang Y, ... & Chen CH. (2017). Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nature genetics*, 49(1), 152–156.
20. Nagel M, Jansen PR, Stringer S, Watanabe K, De Leeuw CA, Bryois J, ... & Posthuma D. (2018). Meta-analysis of genome-wide association studies for neuroticism in 449,484 individuals identifies novel genetic loci and pathways. *Nature genetics*, 50(7), 920–927.
21. Karlsson Linnér R, Mallard TT, Barr PB, Sanchez-Roige S, Madole JW, Driver MN, ... & Dick DM. (2021). Multivariate analysis of 1.5 million people identifies genetic associations with traits related to self-regulation and addiction. *Nature neuroscience*, 24(10), 1367–1376.
22. Vukasović T, & Bratko D. (2015). Heritability of personality: A meta-analysis of behavior genetic studies. *Psychological bulletin*, 141(4), 769.
23. Keller MC, Coventry WL, Heath AC, & Martin NG. (2005). Widespread evidence for non-additive genetic variation in Cloninger's and Eysenck's personality dimensions using a twin plus sibling design. *Behavior genetics*, 35(6), 707–721.
24. Markel G, Beauchamp J, Ahlskog R, Ebeltoft JC, Möttus R, Oskarsson S, ... & Ystrom E. (2025). Nature, nurture, and socioeconomic outcomes: New evidence from sib pairs and molecular genetic data. Available at SSRN.
25. Yengo L, Liang Y, 23andMe Research Team, Wang X., Granka JM., Evans DM., ... & Visscher PM. (2025). Within-family heritability estimates for behavioural and disease phenotypes from 500,000 sibling pairs of diverse ancestries. *medRxiv*, 2025-09.
26. Bleidorn W, Schwaba T, Zheng A, Hopwood CJ, Sosa SS, Roberts BW, & Briley DA. (2022). Personality stability and change: A meta-analysis of longitudinal studies. *Psychological bulletin*, 148(7–8), 588–619.
27. Ebert T, Gebauer JE, Brenner T, Bleidorn W, Gosling SD, Potter J, & Rentfrow PJ. (2022). Are regional differences in psychological characteristics and their correlates robust? Applying spatial-

analysis techniques to examine regional variation in personality. *Perspectives on psychological science*, 17(2), 407–441.

28. DeYoung CG, Grazioplene RG, & Allen TA. (2021). The neurobiology of personality. In John OP & Robins RW. (Eds.), *Handbook of personality: Theory and research* (pp. 193–216). The Guilford Press.
29. Depue RA, & Collins PF. (1999). Neurobiology of the structure of personality: Dopamine, facilitation of incentive motivation, and extraversion. *Behavioral and brain sciences*, 22(3), 491–517.
30. Young AI, Nehzati SM, Benonisdottir S, Okbay A, Jayashankar H, Lee C, ... & Kong A. (2022). Mendelian imputation of parental genotypes improves estimates of direct genetic effects. *Nature genetics*, 54(6), 897–905.
31. Turley P, Martin AR, Goldman G, Li H, Kanai M, Walters RK, ... & Neale BM. (2021). Multi-ancestry meta-analysis yields novel genetic discoveries and ancestry-specific associations. *BioRxiv*, 2021-04.
32. Park HH, Wiernik BM, Oh IS, Gonzalez-Mulé E, Ones DS, & Lee Y. (2020). Meta-analytic five-factor model personality intercorrelations: Eeny, meeny, miney, moe, how, which, why, and where to go. *Journal of Applied Psychology*, 105(12), 1490.
33. Forde A, Hemani G, & Ferguson J. (2023). Review and further developments in statistical corrections for Winner's Curse in genetic association studies. *PLoS genetics*, 19(9), e1010546.
34. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics Consortium, ... & Neale BM. (2015). LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature genetics*, 47(3), 291–295.
35. Spearman C. (1910). Correlation calculated from faulty data. *British journal of psychology*, 3(3), 271.
36. Tucker-Drob EM. (2017). Measurement error correction of genome-wide polygenic scores in prediction samples. *BioRxiv*, 165472.
37. Grotzinger AD, Rhemtulla M, de Vlaming R, Ritchie SJ, Mallard TT, Hill WD, ... & Tucker-Drob EM. (2019). Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nature human behaviour*, 3(5), 513–525.
38. Casey BJ, & Caudle K. (2013). The teenage brain: Self control. *Current directions in psychological science*, 22(2), 82–87.
39. Romer D, Reyna VF, & Satterthwaite TD. (2017). Beyond stereotypes of adolescent risk taking: Placing the adolescent brain in developmental context. *Developmental cognitive neuroscience*, 27, 19–34.
40. Penke L, & Jokela M. (2016). The evolutionary genetics of personality revisited. *Current opinion in psychology*, 7, 104–109.
41. Zietsch BP. (2024). Genomic findings and their implications for the evolutionary social sciences. *Evolution and human behavior*, 45(4), 106596.
42. Lloyd-Jones LR, Zeng J, Sidorenko J, Yengo L, Moser G, Kemper KE, ... & Visscher PM. (2019). Improved polygenic prediction by Bayesian multiple regression on summary statistics. *Nature communications*, 10(1), 5086.
43. Alemu R, Terskaya A, Howell M, Guan J, Sands H, Kleinman A, ... & Estonian Biobank Research Team. (2025). An updated polygenic index repository: expanded phenotypes, new cohorts, and improved causal inference. *bioRxiv*.
44. Wang Y, Kanai M, Tan T, Kamariza M, Tsuo K, Yuan K, ... & Martin AR. (2023). Polygenic prediction across populations is influenced by ancestry, genetic architecture, and methodology. *Cell genomics*, 3(10).
45. Tucker-Drob EM. (2017). How do individual experiences aggregate to shape personality development? *European Journal of Personality*, 31, 570–571.
46. Scarr S, & McCartney K. (1983). How people make their own environments: A theory of genotype→environment effects. *Child development*, 424–435.

47. Torvik FA, Eilertsen EM, Hannigan LJ, Cheesman R, Howe LJ, Magnus P, ... & Ystrom E. (2022). Modeling assortative mating and genetic similarities between partners, siblings, and in-laws. *Nature communications*, 13(1), 1108.
48. Horwitz TB, Balbona JV, Paulich KN, & Keller MC. (2023). Evidence of correlations between human partners based on systematic reviews and meta-analyses of 22 traits and UK Biobank analysis of 133 traits. *Nature human behaviour*, 7(9), 1568–1583.
49. Grosz MP, Rohrer JM, & Thoemmes F. (2020). The taboo against explicit causal inference in nonexperimental psychology. *Perspectives on psychological science*, 15(5), 1243–1255.
50. Bailey DH, Jung AJ, Beltz AM, Eronen MI, Gische C, Hamaker EL, ... & Murayama K. (2024). Causal inference on human behaviour. *Nature human behaviour*, 8(8), 1448–1459.
51. Nivard MG, Belsky DW, Harden KP, Baier T, Andreassen OA, Ystrøm E, ... & Lyngstad TH. (2024). More than nature and nurture, indirect genetic effects on children's academic achievement are consequences of dynastic social processes. *Nature human behaviour*, 8(4), 771–778.
52. Veller C, & Coop GM. (2024). Interpreting population-and family-based genome-wide association studies in the presence of confounding. *PLoS biology*, 22(4), e3002511.
53. Okbay A, Wu Y, Wang N, Jayashankar H, Bennett M, Nehzati SM, ... & Young AI. (2022). Polygenic prediction of educational attainment within and between families from genome-wide association analyses in 3 million individuals. *Nature genetics*, 54(4), 437–449. 23
54. Madole JW, & Harden KP. (2023). Building causal knowledge in behavior genetics. *Behavioral and Brain Sciences*, 46, e182.
55. National Academies of Sciences, Engineering, and Medicine. (2023). Using population descriptors in genetics and genomics research: A new framework for an evolving field. Washington, DC: The National Academies Press. 10.17226/26902.
56. Turner S, Armstrong LL, Bradford Y, Carlson CS, Crawford DC, Crenshaw AT, ... & Ritchie MD. (2011). Quality control procedures for genome-wide association studies. *Current protocols in human genetics*, 68(1), 1–19.
57. The 1000 Genomes Project Consortium. (2015). A global reference for human genetic variation. *Nature*, 526, 68–74.
58. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, & Lee JJ. (2015). Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience*, 4(1), s13742–015.
59. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, ... & Sham PC. (2007). PLINK: a tool set for whole-genome association and population-based linkage analyses. *The American journal of human genetics*, 81(3), 559–575.
60. Yang J, Lee SH, Goddard ME, & Visscher PM. (2011). GCTA: a tool for genome-wide complex trait analysis. *The american journal of human genetics*, 88(1), 76–82.
61. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjálmsson BJ, Finucane HK, Salem RM, ... & Price AL. (2015). Efficient Bayesian mixed-model analysis increases association power in large cohorts. *Nature genetics*, 47(3), 284–290.
62. Jiang L, Zheng Z, Qi T, Kemper KE, Wray NR, Visscher PM, & Yang J. (2019). A resource-efficient tool for mixed model association analysis of large-scale data. *Nature genetics*, 51(12), 1749–1755.
63. Winkler TW, Day FR, Croteau-Chonka DC, Wood AR, Locke AE, Mägi R, ... & Genetic Investigation of Anthropometric Traits (GIANT) Consortium. (2014). Quality control and conduct of genome-wide association meta-analyses. *Nature protocols*, 9(5), 1192–1212.
64. R Core Team (2023). *_R_: A Language and Environment for Statistical Computing_*. R Foundation for Statistical Computing, Vienna, Austria.
65. Watanabe K, Taskesen E, Van Bochoven A, & Posthuma D. (2017). Functional mapping and annotation of genetic associations with FUMA. *Nature communications*, 8(1), 1826.
66. Reich DE, Cargill M, Bolk S, Ireland J, Sabeti PC, Richter DJ, ... & Lander ES. (2001). Linkage disequilibrium in the human genome. *Nature*, 411(6834), 199–204.
67. O'Connor LJ, Schoech AP, Hormozdiari F, Gazal S, Patterson N, & Price AL. (2019). Extreme polygenicity of complex traits is explained by negative selection. *The American journal of human genetics*, 105(3), 456–476.

68. Brown BC, Ye CJ, Price AL, & Zaitlen N. (2016). Transethnic genetic-correlation estimates from summary statistics. *The American Journal of Human Genetics*, 99(1), 76–88.
69. Viechtbauer W. (2010). Conducting meta-analyses in R with the metafor package. *Journal of statistical software*, 36, 1–48. John, O. P., Donahue, E. M., & Kentle, R. (1991). *The Big Five Inventory*. Technical report, University of California, Berkeley
70. Zakrisson I. (2010). *Big Five Inventory (BFI): Utprövning för svenska förhållanden*. Mid Sweden University.
71. Mullins-Sweatt SN, Jamerson JE, Samuel DB, Olson DR, & Widiger TA. (2006). Psychometric properties of an abbreviated instrument of the five-factor model. *Assessment*, 13(2), 119–137.
72. Rammstedt B, Kemper CJ, Klein MC, Beierlein C, & Kovaleva A. (2013). A short scale for assessing the big five dimensions of personality: 10 item big five inventory (BFI-10). *methods, data, analyses*, 7(2), 17.
73. Costa PT, & McCrae RR. (1992). *Professional manual for the NEO-PI-R and NEO-FFI*. Odessa, FL: Psychological Assessment Resources.
74. Björnsdóttir G, Jonsson FH, Hansdóttir I, Almarsdóttir AB, Heimisdóttir M, Tyrfingsson T, ... & Thorgeirsson TE. (2014). Psychometric properties of the Icelandic NEO-FFI in a general population sample compared to a sample recruited for a study on the genetics of addiction. *Personality and individual differences*, 58, 71–75.
75. Ostendorf F & Angleitner A. (2004). *NEO-Persönlichkeitsinventar nach Costa und McCrae, Revidierte Fassung (NEO-PI-R): Hogrefe Göttingen*.
76. Terracciano A. (2003). The Italian version of the NEO PI-R: conceptual and empirical support for the use of targeted rotation. *Personality and Individual Differences*, 35, 1859–1872.
77. Hoekstra HA, Ormel J, & De Fruyt F. (1996). *Manual of the Dutch version of the NEO-PI-R/ NEO-FFI*.
78. Goldberg LR. (1992). The development of markers for the Big-Five factor structure. *Psychological Assessment*, 4(1), 26–42.
79. Goldberg LR. (1999). A broad-bandwidth, public domain, personality inventory measuring the lower-level facets of several five-factor models. In Mervielde I, Deary IJ, De Fruyt F, & Ostendorf F. (Eds.). *Personality Psychology in Europe*, Vol. 7, Tilburg University Press, Tilburg.
80. Henry S, & Möttus R. (2023). The 100 nuances of personality: Development of a comprehensive, non-redundant personality item pool. 10.17605/OSF.IO/TCFGZ
81. Eysenck HJ, & Eysenck SB. (1968). *Eysenck personality inventory*. *Journal of Clinical Psychology*.
82. Eysenck HJ, Eysenck SBG. (1994). *Manual of the Eysenck Personality Questionnaire: (EPQ-R adult)*. EdITS/Educational and Industrial Testing Service.
83. Sidorenko J, Kassam I, Kemper KE, Zeng J, Lloyd-Jones LR, Montgomery GW, ... & Visscher PM. (2019). The effect of X-linked dosage compensation on complex trait variation. *Nature communications*, 10(1), 3009.
84. Lee JJ, Wedow R, Okbay A, Kong E, Maghzian O, Zacher M, ... & Cesarini D. (2018). Gene discovery and polygenic prediction from a genome-wide association study of educational attainment in 1.1 million individuals. *Nature genetics*, 50(8), 1112–1121.
85. Clapp Sullivan ML, Schwaba T, Harden KP, Grotzinger AD, Nivard MG, & Tucker-Drob EM. (2024). Beyond the factor indeterminacy problem using genome-wide association data. *Nature human behaviour*, 8(2), 205–218.
86. De Leeuw CA, Mooij JM, Heskes T, & Posthuma D. (2015). MAGMA: generalized gene-set analysis of GWAS data. *PLoS computational biology*, 11(4), e1004219.
87. Akingbuwa WA, Hammerslag AR, Bartels M, Nivard MG, & Middeldorp CM. (2022). Ultra-rare and common genetic variant analysis converge to implicate negative selection and neuronal processes in the aetiology of schizophrenia. *Molecular psychiatry*, 27(9), 3699–3707.
88. Ruan Y, Lin YF, Feng YCA, Chen CY, Lam M, Guo Z, ... & Ge T. (2022). Improving polygenic prediction in ancestrally diverse populations. *Nature genetics*, 54(5), 573–580.
89. Benjamini Y, & Hochberg Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal statistical society: series B (methodological)*, 57(1), 289–300.

90. Rosseel Y. (2012). lavaan: An R package for structural equation modeling. *Journal of statistical software*, 48(1), 1–36.
91. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, ... & Haycock PC. (2018). The MR-Base platform supports systematic causal inference across the human phenome. *elife*, 7, e34408.
92. Sanderson E, Glymour MM, Holmes MV, Kang H, Morrison J, Munafò MR, ... & Davey Smith G. (2022). Mendelian randomization. *Nature reviews methods primers*, 2(1), 6.
93. Hartwig FP, Davey Smith G, & Bowden J. (2017). Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *International journal of epidemiology*, 46(6), 1985–1998.
94. Bowden J, Davey Smith G, Haycock PC, & Burgess S. (2016). Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genetic epidemiology*, 40(4), 304–314.
95. Ennis G, Williams C, Mallard TT, Schwaba T, de la Fuente J, & Tucker-Drob EM. (2025). Genomic taxometric analysis of negative emotionality and major depressive disorder highlights a gradient of genetic differentiation across the severity spectrum. *MedRxiv*

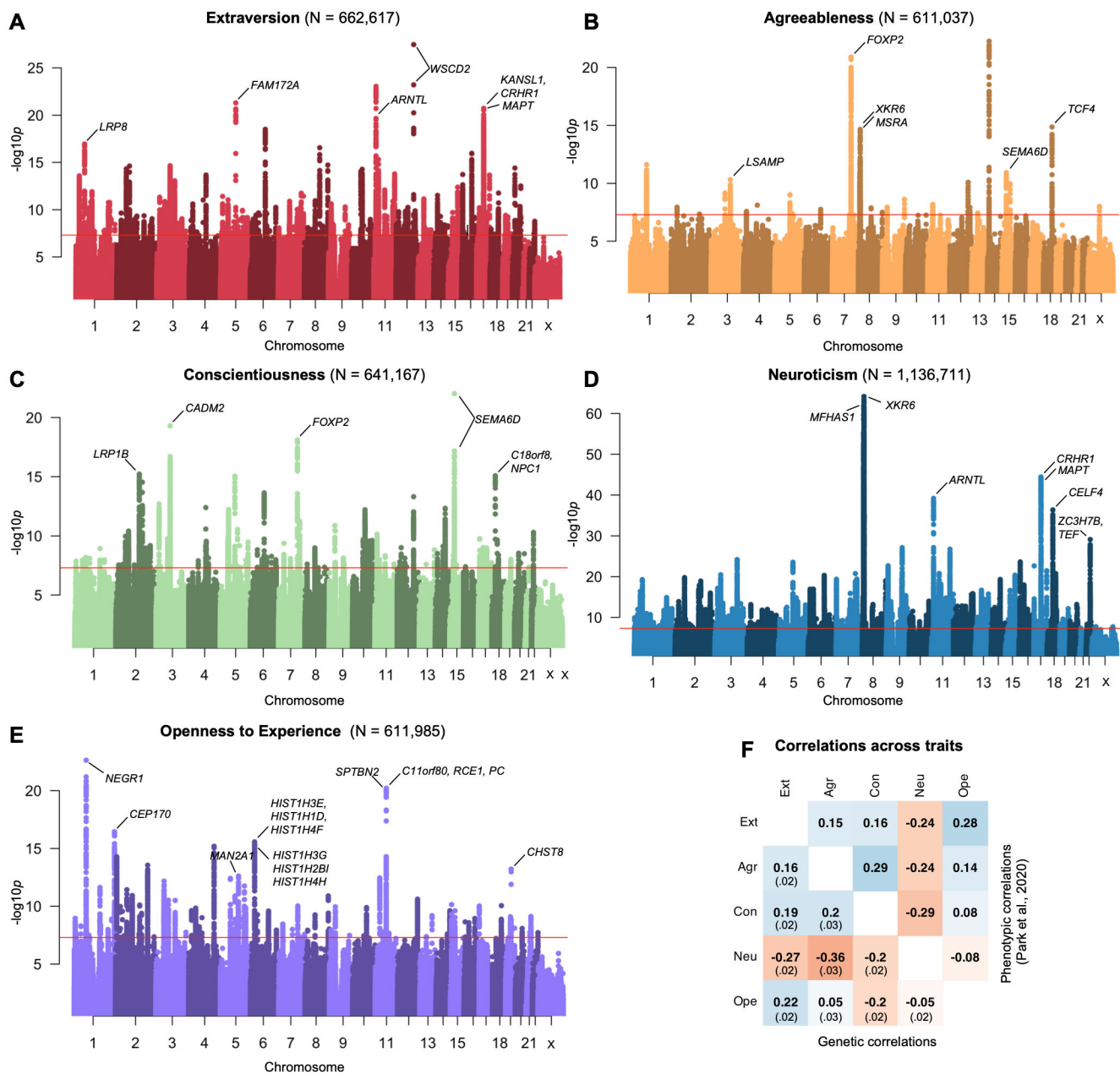


Figure 1. Genome-Wide associations with the Big Five personality traits. Panels A-E depict Manhattan plots of genetic associations for each Big Five personality trait. Points correspond to two-sided test p-values of GWAS regressions. Genome wide significance is denoted with a red line corrected for multiple comparisons at $p = 5 \times 10^{-8}$. A selection of genes containing or nearby the most significant lead SNPs are annotated in each panel (Supplementary Tables S30–S34). Panel F depicts correlations among the Big Five personality traits. Below-diagonal are genetic correlations among participants with EUR-like genomes estimated using LDSC; above-diagonal are meta-analytic phenotypic correlations from Park and colleagues (2020). Standard errors are in parentheses.

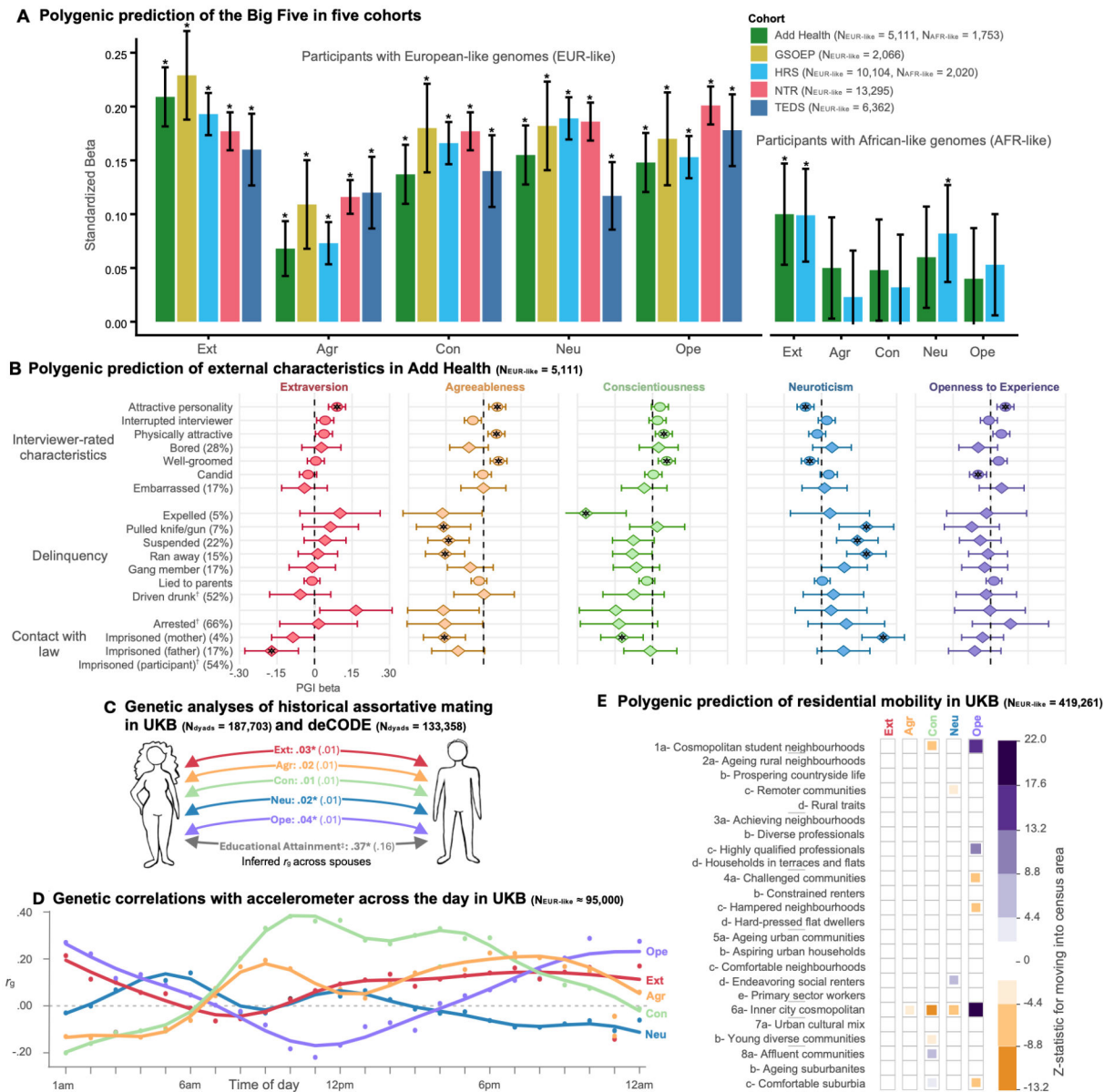


Figure 2. Polygenic prediction and additional genetic associations.

Ext = Extraversion. Agr = Agreeableness. Con = Conscientiousness. Neu = Neuroticism.

Ope = Openness to Experience. Panel A depicts standardized beta point estimates for

regression-model prediction of phenotypic personality traits among participants with EUR-like and AFR-like genomes in five cohorts using PGI weights derived from the EUR-like population-level GWAS. Numerical results are provided in Supplementary Table S35. Panel

B depicts polygenic prediction of external phenotypes among participants with EUR-like genomes. In this panel, point estimates for regression-model prediction of continuous traits are standardized betas depicted with circles, and estimates for binary traits are logistic betas depicted with diamonds; percentage affirmative responses are noted in parentheses. † =

questions administered only to a subset of participants (see Supplementary Text). Numerical results are provided in Supplementary Table S39. Panel C depicts meta-analytic correlations

between PGIs for each pair of family members, disattenuated for measurement error using structural equation models and scaled to represent the inferred genetic similarity among parents. ‡ = Educational Attainment estimates come from Torvik et al. (2022), estimated across spouses in the MoBa cohort. Numerical results are provided in Supplementary Table S40. Panel D depicts genetic correlations with accelerometer activity, which indexes physical movement across a 24-hour period; see Grotzinger et al. (2022b) for complete details. Panel E depicts polygenic associations with census area of residence at age 50+, controlling for birthplace in addition to sex, age, array, and genetic principal components. In this panel, only associations that are significant at $p < .01$ after application of Benjamini-Hochberg false-discovery rate correction and sign-concordant within sibship are plotted. In all panels, error bars depict 95% confidence intervals. * = $p < .01$ from a two-sided test with no correction for multiple comparisons.



Figure 3. Population-level genetic correlations between the Big Five personality traits and 67 behaviors and outcomes across 9 domains.

E = Extraversion. A = Agreeableness. C = Conscientiousness. N = Neuroticism. O = Openness to experience. COVID = Coronavirus disease. HDL = High-density lipoprotein. LDL = Low-density lipoprotein. ADHD = Attention deficit hyperactivity disorder. Letters corresponding to personality traits represent point estimates of the genetic correlation. Error bars represent 95% confidence intervals. Associations are depicted in gray when not significant with two-sided test $p < .01$ and no further correction for multiple testing. Associations estimated using LDSC among participants with EUR-like genomes. Descriptions of each phenotype and numerical results are available in Supplementary Tables S37 and S38.

Comparison estimates for Educational Attainment (EA) come from a PGI constructed from the Okbay et al. (2022) GWAS of EA with deCODE and 23&Me cohorts held out. In both Panels A and B, point estimates are standardized betas from regressions predicting phenotypic personality traits using PGI weights derived from the EUR-like population-level GWAS. Panel C depicts h^2_{SNP} estimates estimated with LDSC from the within-family GWAS (“Wit.”), presented alongside full EUR-like population-level GWAS (“Full pop.,” Table 1) and matched population-level (“Pop.”) GWAS in cohorts that contributed to within-family GWAS (Supplementary Table S46). r_g below each pair of traits indicates their genetic correlation estimated with LDSC, with deviation from $r_g = 1$ tested using a nested chi-square model in Genomic SEM. p -values above each pair of traits indicates results of a test for differences in heritability between population and within-family estimates. In all panels, error bars depict 95% confidence intervals and standard errors are in parentheses, and p -values correspond to two-sided tests with no correction for multiple testing. $ns = p \geq .05$. * = $p < .05$. ** = $p < .01$. *** = $p < .001$.

Table 1.

Summary of Population-Level Genome-Wide Association Study Results

Trait	N _{Total} (N _{AFR-like})	Mean χ^2	Previous Lead SNPs	This Study Lead SNPs	LDSC Intercept EUR/ AFR- like	EUR-like h^2_{SNP} and cross-cohort r_g				Mean LDSC r_g across EUR-like cohorts grouped by:				
						LDSC h^2_{SNP} estimate GWAS	Meta- analyzed individual h^2_{SNP} estimates	Disattenuated for typical/all measurement instrument error	Mean cross- cohort r_g	Geographic region	Measurement instrument	Reporter perspective	Military service	Age
Extraversion	662,617/43,201	1.58	17	258	1.00/1.01	9.3% (0.3)	10.6% (1.3)	13.3% (0.6)/ 15.8% (0.9)	.71	.91	.87	.92	.85	1.0
Agreeableness	611,037/43,482	1.29	4	39	1.02/1.00	4.8% (0.2)	7.4% (1.0)	9.3% (0.6)/ 10.8% (0.9)	.45	.65	.61	.95	.73	.69
Conscientiousness	641,167/43,120	1.44	3	131	1.03/1.02	7.1% (0.2)	7.9% (1.0)	9.6% (0.6)/ 11.2% (0.8)	.72	.86	.91	.68	.79	.78
Neuroticism	1,136,711/48,110	2.01	224	706	0.99/1.02	8.3% (0.3)	8.4% (0.8)	9.6% (0.4)/ 12.0% (0.8)	.73	.99	.94	.77	.84	.73
Openness to experience	611,985/43,498	1.43	8	126	1.03/1.01	7.4% (0.3)	9.4% (1.6)	12.9% (0.8)/ 15.2% (1.0)	.67	.92	.83	.87	.78	.88

Note. h^2_{SNP} = Single Nucleotide Polymorphism (SNP) heritability estimated using LDSC. EUR-like = Individuals with European-like genomes, as measured by genetic similarity to reference panels. AFR-like = Individuals with African-like genomes, as measured by genetic similarity to reference panels. LDSC = Linkage Disequilibrium Score regression. Lead SNPs = number of genome-wide significant SNPs (from regression predicting trait from SNP, from two-sided test with multiple testing correction of $p < 5 \times 10^{-8}$) that are independent (Linkage Disequilibrium $r^2 < .10$) of other lead SNPs within 250kb. Numbers in parentheses represent standard errors. Genetic correlations estimated using LDSC. Correlations across geographic regions span US, continental Europe, Nordic, UK/Australia; correlations across age groups span younger (age ≤ 25), midlife (25–64) and older adults (65+).