Article

Robust inference and correlates from genetic associations with personality

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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, their generalizability and the biological and social pathways through which they act. Here we meta-analyse data across 46 cohorts comprising 611,037 to 1.14 million 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 up to 50,725 participants for within-family GWAS. We identify 1,260 lead genetic variants associated with personality, including 824 novel variants[3]. Common genetic variants explain a moderate 4.8–9.3% of the variance in measures of each trait, and 9.3–13.3% among instruments with typical measurement reliability. Genetic associations with personality are highly consistent but not identical across geography, reporter (self versus 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 behavioural 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 behaviours and life outcomes. Overall, we find that the genetic architecture of personality is robustly generalizable, minimally confounded and widely relevant to human experience.

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 labour 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 behaviour and life outcomes.

Here we report meta-analytic GWAS results from the Revived Genomics of Personality Consortium (ReGPC), a collaboration across 46 cohorts incorporating between 611,037 and 1.14 million participants per Big Five trait. We also provide a frequently asked questions 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 work[18] from 3 to 131 for conscientiousness, from 4 to 39 for agreeableness, from 8 to 126 for openness to experience, from 14 to 258 for extraversion and from 224 to 706 for neuroticism. The additive effects tagged by the common genetic variants (single-nucleotide polymorphism (SNP) heritability, h^2_{SNP}) account for an estimated 4.8–16.2% of total personality variation across traits and models. This is consistent with previous GWAS of personality[3,19–22] 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 around 40% to 60%[18,23–25]. 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. Although 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 versus 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 behavioural 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 behaviours and life outcomes ranging from psychopathology

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Table 1 | Summary of population-level GWAS results

						EUR-like h^2_{SNP} and cross-cohort r_g				Mean LDSC r_g across EUR-like cohorts grouped by:				
Trait	n_{Total}; $n_{AFR\text{-}like}$	**Mean χ^2**	**Previous lead SNPs**	**Lead SNPs in this study**	**LDSC intercept (EUR-like; AFR-like)**	**LDSC h^2_{SNP} estimate from GWAS**	**Meta-analysed individual h^2_{SNP} estimates**	**Disattenuated for measurement instrument error (typical; all)**	**Mean cross-cohort r_g**	**Geographical 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%)	0.71	0.91	0.87	0.92	0.85	1.00
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%)	0.45	0.65	0.61	0.95	0.73	0.69
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%)	0.72	0.86	0.91	0.68	0.79	0.78
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%)	0.73	0.99	0.94	0.77	0.84	0.73
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%)	0.67	0.92	0.83	0.87	0.78	0.88

h^2_{SNP} was estimated using LDSC. The lead SNP columns represent the number of genome-wide significant SNPs (from regression predicting trait from SNP, using two-sided test with multiple-testing correction ($P < 5\times10^{-8}$)) that are independent (linkage disequilibrium $r^2 < 0.10$) of other lead SNPs within 250 kb. The numbers in parentheses represent s.e. values. Genetic correlations were estimated using LDSC. Correlations across geographical regions span the USA, continental Europe, Nordic, the UK–Australia. Correlations across age groups span younger (≤25 years), mid-life (25–64 years) and older adults (65 years or older).

and physical health to research participation and residential mobility, highlighting a central role of personality in understanding the human experience.

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 European-like (EUR-like) ($k_{cohorts} = 46$) and African-like (AFR-like) ($k_{cohorts} = 10$) genomes, as measured by genetic similarity to reference panels (Supplementary Tables 1–3 and Supplementary Notes 1 and 2). We jointly analysed results using inverse variance-weighted meta-analysis (IVW), supplemented with multi-ancestry meta-analysis (MAMA)[31], resulting in pooled associations for around 10 million SNPs for each Big Five trait.

We identified 1,260 approximately independent ($r^2 < 0.10$ within a 250 kb 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 and Supplementary Tables 4–13). Of the 1,260 lead SNPs, 824 (65%) were found in novel 250 kb loci that had not previously been associated with variation in the respective trait. Manhattan plots of IVW results are displayed in Fig. 1a–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 14), and the average absolute genetic correlation among Big Five traits among participants with EUR-like genomes was 0.19 (Fig. 1f (below the diagonal)), similar to phenotypic correlations[32] (Fig. 1f (above the 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 (r_g) between the two (mean $r_g = 0.94$) (Supplementary Table 15). Individual SNP effects were extremely small, reflecting the highly distributed genetic architecture of personality. For example, the median association estimate among extraversion lead SNPs, corrected for the winner's curse[33], is 0.009 s.d. per effect allele (corresponding to scoring at the 50.35th versus the 50th percentile in extraversion). On average, the estimated effective number of independently associated common SNPs for each trait was 16,180 (Supplementary Table 17). We provide additional GWAS results, including genetic ancestry-stratified analyses and comparisons illustrating similarity between IVW and MAMA estimates, in Extended Data Fig. 1 and Supplementary Tables 16–20.

Characterizing SNP heritability

Among participants with EUR-like genomes, SNP heritability (h^2_{SNP}) estimated for the Big Five traits using linkage disequilibrium score regression (LDSC)[34] ranged from 4.8% (s.e. = 0.2%) for agreeableness to 9.3% (s.e. = 0.3%) for extraversion (Table 1, Supplementary Table 4 and 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% (s.e. = 0.6%) across traits (ranging from 7.4% for agreeableness to 10.6% for extraversion; Table 1 and Supplementary Table 21), with significant variability across cohorts (mean $\tau = 3.6\%$). Random response error by the participants cannot systematically relate to their genome[35,36]. Accordingly, we found that personality measures with greater reliability (lower random response error) tended to be more heritable ($b = 6.7\%$, s.e. = 0.7%; Extended Data Fig. 2). In this analysis, the expected h^2_{SNP} for a measure of typical (median) reliability ($\alpha = 0.81$) ranged from 9.3% for agreeableness (s.e. = 0.6%) to 13.3% for extraversion (s.e. = 0.6%), and h^2_{SNP} completely disattenuated for measurement error ranged from 10.8% for agreeableness (s.e. = 0.9%) to 15.8% for extraversion (s.e. = 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 and Extended Data Fig. 3). Genetic effects were similar but not identical across four western country clusters (USA, continental Europe, Nordic and UK–Australia, mean $r_g = 0.86$, mean s.e. = 0.15), three age groups (young (≤25 years), middle (25–64 years) and older (65 years and older), mean $r_g = 0.80$, mean s.e. = 0.18), between the Million Veteran Program and other, primarily non-veteran cohorts (mean $r_g = 0.82$, mean s.e. = 0.04), and across five personality measurement instruments (mean $r_g = 0.85$, mean s.e. = 0.07). Additional characterization of genetic architecture across measurement instruments using genomic structural equation modelling[37] confirmed that genetic effects plausibly operate at the level of broad cross-instrument latent factors, with only one locus showing significantly heterogenous effects across measurement instruments (Supplementary Tables 22–24 and Extended Data Fig. 4). Notably, genetic associations with agreeableness were less consistent across cohorts (Table 1),

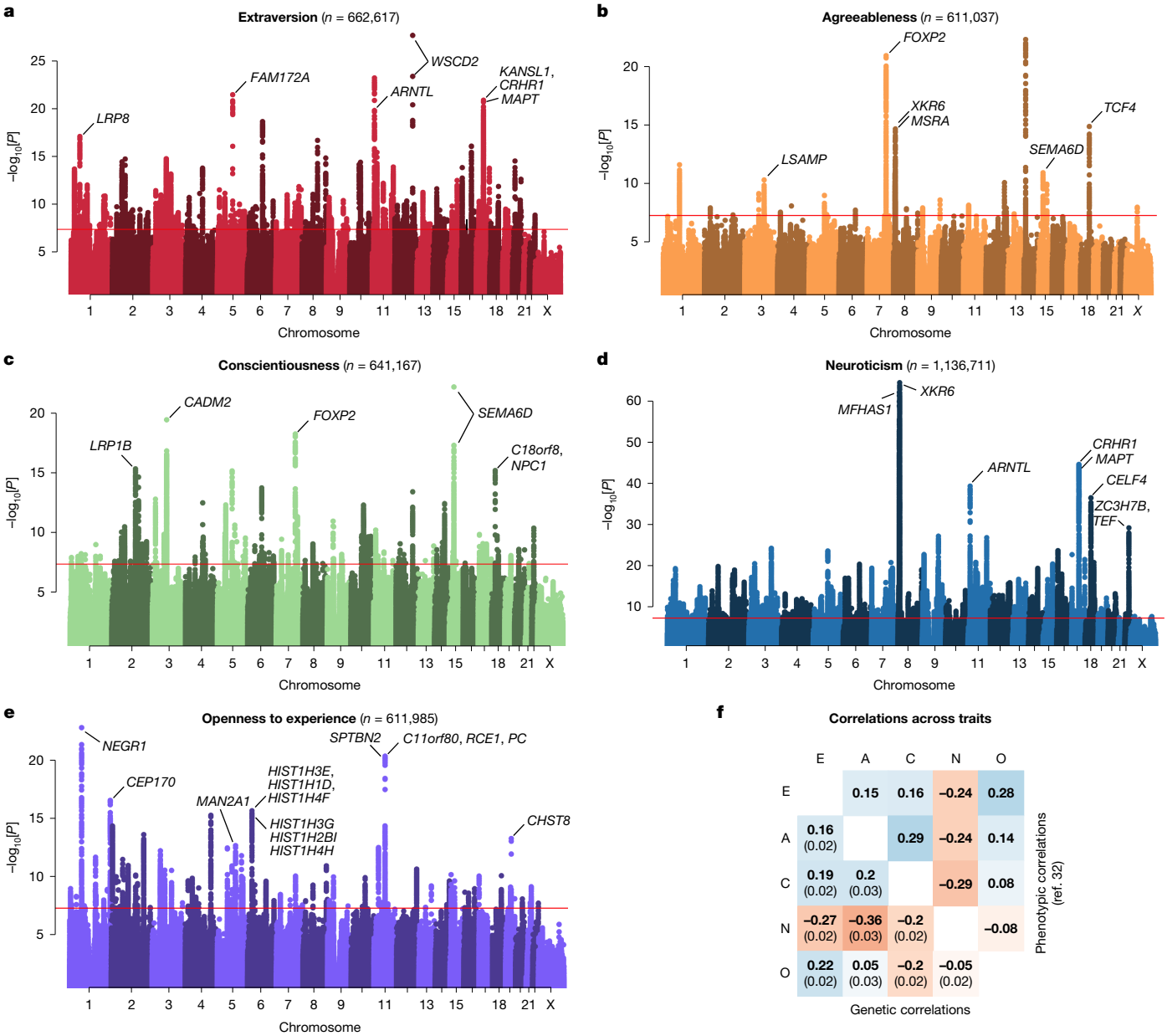

Fig. 1 | Genome-wide associations with the Big Five personality traits. **a**–**e**, Manhattan plots of genetic associations for each Big Five personality trait: extraversion (**a**; $n = 662{,}617$), agreeableness (**b**; $n = 611{,}037$), conscientiousness (**c**; $n = 641{,}167$), neuroticism (**d**; $n = 1{,}136{,}711$) and openness to experience (**e**; $n = 611{,}985$). The points correspond to two-sided test P values of GWAS regressions. Genome-wide significance is denoted by 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 30–34). **f**, Correlations among the Big Five personality traits. Genetic correlations estimated using LDSC among participants with EUR-like genomes are below the diagonal; meta-analytic phenotypic correlations from ref. 32 are above the diagonal. Standard errors are shown in parentheses. A, agreeableness; C, conscientiousness; E, extraversion; N, neuroticism; O, openness to experience.

explaining in part why agreeableness exhibited lower heritability than other traits in the meta-analytic GWAS. In the Estonian Biobank, in which the personality of the participants was assessed both by their self-report ($n = 73{,}983$) and by reports by close others ($n = 20{,}269$), we found strong genetic overlap between rater perspectives (mean $r_g = 0.84$, mean s.e. = 0.12), indicating that the genetic architecture of personality is not an epiphenomenon of self-perception. In sex-stratified analyses of neuroticism in the UK Biobank cohort, X-chromosome-linked h^2_{SNP} did not differ between male individuals ($n = 168{,}989$; $h^2_{SNP,X} = 0.23\%$; s.e. = 0.04%) and female individuals ($n = 198{,}139$; $h^2_{SNP,X} = 0.18\%$; s.e. = 0.03%; $P_{difference} = 0.33$). The dosage compensation ratio ($\hat{\gamma} = 1.26$, s.e. = 0.30) was intermediate between no compensation (0.5) and full compensation (2.0) but was estimated relatively imprecisely. Genetic effects were correlated near-unity across sex ($r_g = 0.96$; 95% confidence interval (CI) = 0.81–1.10).

Biological follow-up of GWAS signals indicated that enriched gene sets intersected across the Big Five (mean enrichment rank-order $\rho = 0.72$; Extended Data Fig. 5), providing evidence for trait-overlapping molecular and cellular systems in personality neurobiology despite only modest genetic correlations (Fig. 1f). Consistent with theories of personality development that emphasize the prefrontal cortex[38,39], genetic associations for each Big Five trait, except for agreeableness, were enriched in genes expressed in the prefrontal cortex (among these, top lead SNPs implicate *RCE1*, *FOXP2* and *SEMA6D*, indicated in Fig. 1; Supplementary Tables 25–34). All traits demonstrated strong enrichment in protein-truncating variant-intolerant gene sets

specifically expressed in neurons (such as *ARNTL*, *TCF4* and *NEGR1*; Fig. 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 aetiology to variation in openness to experience and extraversion, and serotonergic aetiology 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 25–29), suggesting that 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 PGIs. PGI weights were constructed using our EUR-like discovery GWAS with SBayesR[42]. 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 0.097 (0.005) for agreeableness to 0.189 (0.005) for extraversion; Fig. 2a, Supplementary Tables 35 and 36 and 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 Health and Retirement Study 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 samples[44]. Nevertheless, PGIs significantly predicted extraversion (meta-analytic $\beta = 0.099$ (0.016)), neuroticism ($\beta = 0.071$ (0.017)) and openness to experience ($\beta = 0.047$ (0.017)) at $P < 0.01$; Fig. 2a and Supplementary Tables 35 and 36), providing the first evidence for significant PGI prediction of personality traits beyond individuals with EUR-like genomes.

Associations with behaviours and outcomes

We quantified the relevance of personality genetics to relevant behaviours 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 Fig. 6.

Genetic correlations

Genetic correlations estimated using LDSC indicate widespread genetic sharing between personality traits and health-relevant daily behaviours. Conscientiousness in particular was genetically correlated with reduced substance use (across substances, mean $r_g = -0.21$), greater sports frequency ($r_g = 0.35$) and greater preference for low-calorie foods ($r_g = 0.17$), as well as the likely downstream consequences of these behaviours: fewer spells in the hospital ($r_g = -0.21$), healthier ageing ($r_g = 0.14$) and lower body mass index (BMI; $r_g = -0.16$) (Supplementary Tables 37 and 38). Personality was also genetically correlated with fluctuations in accelerometer-measured behaviour across the day, with openness to experience linked to increased night-time activity ($r_g \approx 0.25$) and conscientiousness to increased activity during the day ($r_g \approx 0.30$; Fig. 2d).

We found substantial genetic correlations between the Big Five and each of ten psychiatric disorders and four transdiagnostic psychiatric disorder factors (Fig. 3). Genetic profiles associated with neuroticism were associated with increased risk for all forms of psychopathology (mean cross-disorder $r_g = 0.43$), particularly internalizing disorders (factor $r_g = 0.73$), whereas genetic profiles associated with agreeableness displayed cross-cutting protective associations (mean $r_g = -0.20$). We also identified broad patterns of positive genetic associations between openness and psychopathology (mean $r_g = 0.20$), 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 $r_g = -0.08$) but greater risk for neurodevelopmental disorders (factor $r_g = 0.18$), and conscientiousness genetics were associated with lower risk for neurodevelopmental disorders (factor $r_g = -0.24$) but greater risk for compulsive disorders (factor $r_g = 0.13$). 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 behaviour in the UK Biobank indicated links between personality and research participation (Fig. 3). In particular, genetic variants associated with openness to experience and agreeableness were also associated with completing optional questionnaires (mean $r_g = 0.22$ and 0.11, respectively), whereas genetic variants associated with neuroticism were associated with fewer questionnaire responses ($r_g = -0.23$) and more 'I don't know' and 'prefer no response' answers (mean $r_g = 0.32$) after beginning a questionnaire. The genetics of personality may therefore 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 through nondeterministic transactions with the environment[45,46]. 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 (Fig. 2b and Supplementary Table 39). 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 behaviour and intergenerational contact with the prison system (Fig. 2b and Supplementary Table 39): 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 sociodemographic analysis in the 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 neighbourhoods by middle–older adulthood (age 50 years), whereas genetic profiles indicative of higher conscientiousness predicted greater likelihood of moving away from cosmopolitan areas and into affluent suburban communities (Fig. 2e). We present additional residential mobility analyses focused on urban/rural migration in Extended Data Fig. 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 behaviours and outcomes from personality-relevant

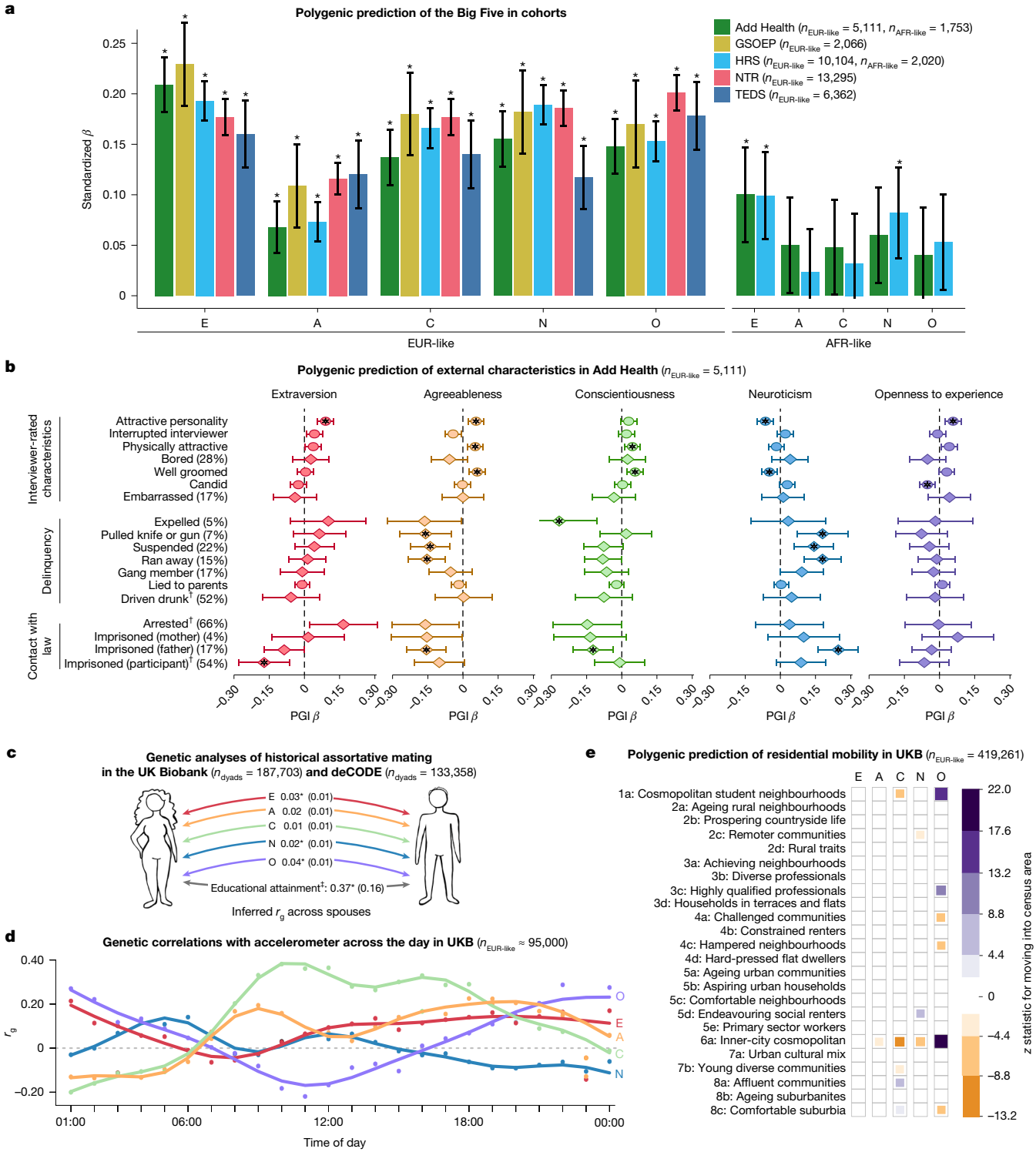

Fig. 2 | Polygenic prediction and additional genetic associations. **a**, Standardized β point estimates for regression model prediction of phenotypic personality traits among participants with EUR-like and AFR-like genomes in five cohorts using PGI weights derived from the EUR-like population-level GWAS. Numerical results are provided in Supplementary Table 35. HRS, Health and Retirement Study. **b**, Polygenic prediction of external phenotypes among participants with EUR-like genomes in the Add Health cohort (n = 5,111). Point estimates for regression-model prediction of continuous traits are standardized β values depicted by circles, and estimates for binary traits are logistic β values depicted with diamonds. For binary traits, the percentage of affirmative responses is noted in parentheses. The dagger symbol (†) indicates questions administered to only a subset of participants (Supplementary Information). Numerical results are provided in Supplementary Table 39. **c**, 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. The double dagger symbol (‡) indicates that educational attainment estimates come from ref. 47, estimated across spouses in the MoBa cohort. Numerical results are provided in Supplementary Table 40. **d**, Genetic correlations with accelerometer activity, which indexes physical movement across a 24 h period, in the UK Biobank. $n_{EUR-like}$ ≈ 95,000. See ref. 55 for complete details. **e**, Polygenic associations with census area of residence at age 50 years and older in the UK Biobank, controlling for birthplace in addition to sex, age, array and genetic principal components. $n_{EUR-like}$ = 419,261. Only associations that are significant at $P < 0.01$ after application of Benjamini–Hochberg false discovery rate correction and that are sign-concordant within sibship are plotted. In **a** and **b**, the error bars depict 95% CIs. *$P < 0.01$, determined using a two-sided regression test with no correction for multiple comparisons.

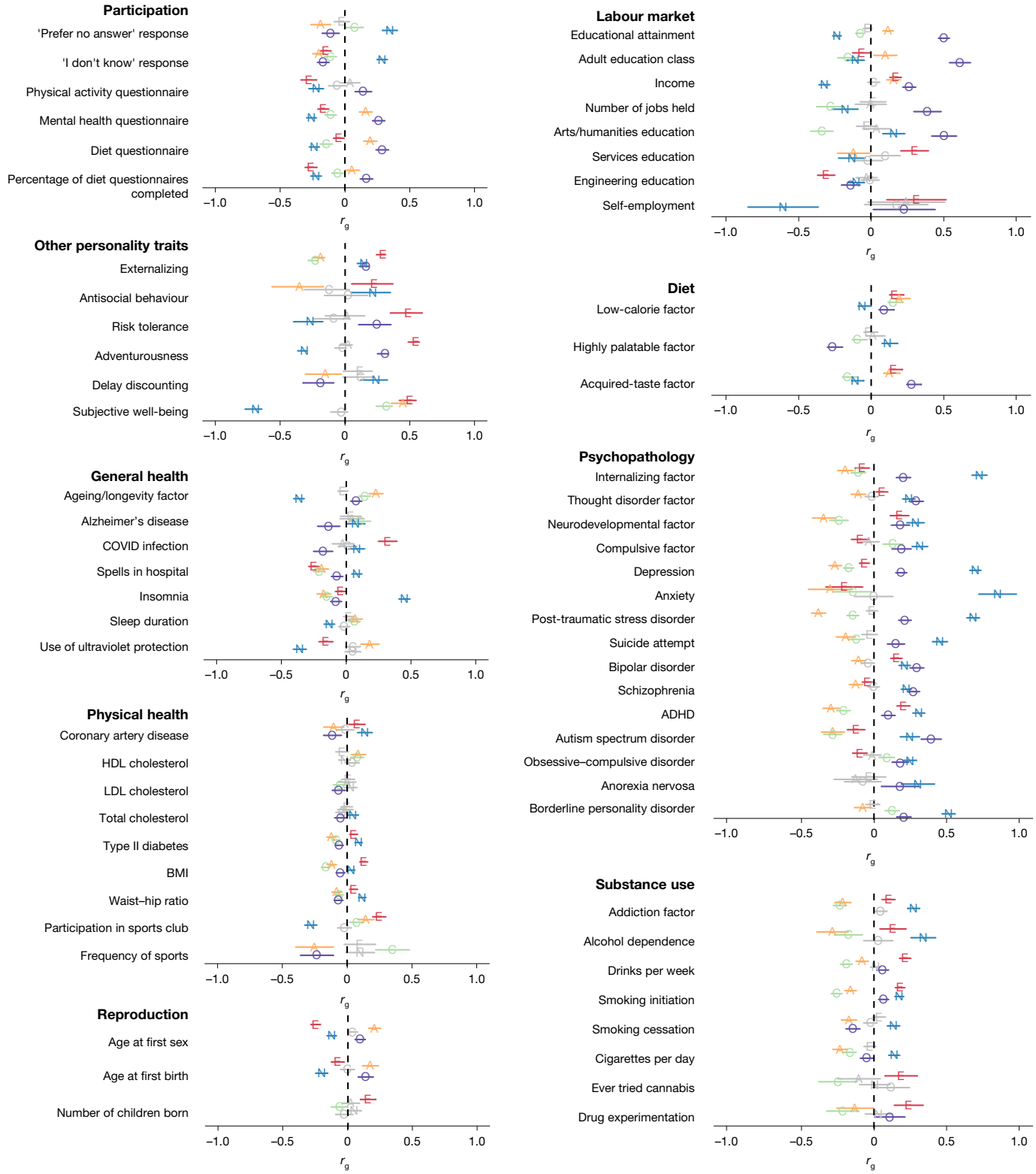

Fig. 3 | Population-level genetic correlations between the Big Five personality traits and 67 behaviours and outcomes across 9 domains. Letters corresponding to personality traits represent point estimates of the genetic correlation. Error bars represent the 95% CIs. Associations are depicted in grey when not significant based on a two-sided test threshold of $P < 0.01$ with no correction for multiple testing. Associations were estimated using LDSC among participants with EUR-like genomes. Descriptions of each phenotype and numerical results are provided in Supplementary Tables 37 and 38. ADHD, attention deficit hyperactivity disorder; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

genetic variants was small in magnitude. These PGIs cannot predict an individual's future behaviour.

We also quantified personality similarity between spouses over recent generations. Inferred genetic correlations between parents, estimated using error-corrected PGI similarity[36] meta-analysed across spouses, sibling pairs and cousin pairs from UK Biobank (n_{pairs} = 187,703) and deCODE (n_{dyads} = 133,358), indicated minimal assortative mating for each of the Big Five traits (estimated parental

r_g = 0.01–0.04; Fig. 2c and Supplementary Table 40). Over past generations, 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 = 0.37)[47,48]. Phenotypic assortative mating estimates between deCODE parents (n_{pairs} = 5,317) were stronger in magnitude but remained small for all traits besides openness to experience (r_s = 0.07–0.12; openness r = 0.18; Extended Data Fig. 8 and Supplementary Table 41), consistent with previous estimates[48].

Mendelian randomization

To test causality and directionality in associations between personality traits and biobehavioural outcomes, we applied MR tests to a subset of 13 outcomes most likely to comport with core assumptions of this method (Supplementary Tables 42 and 43). We found plausible causal effects for 33 exposure–outcome pairings, where effects directionally replicated across MR estimators and multiple 95% CIs excluded 0 (Extended Data Fig. 9). Twenty-four analyses indicated effects of personality on biobehavioural outcomes, providing 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 ageing/longevity factor. Furthermore, consistent with theoretical perspectives that life experiences affect personality development[1,26], we found nine plausibly causal effects of biobehavioural 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 methods[49]. Nevertheless, future work should further triangulate the MR-based causal inferences reported here with additional methods and data that permit strong causal inference[50].

Evaluating familial confounding

Polygenic prediction within families

We used data from the Netherlands Twin Register (NTR) ($n_{families}$ = 2,956) and Twins Early Development Study (TEDS) ($n_{families}$ = 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-analysed across the NTR and TEDS cohorts and averaged across the Big Five, was β = 0.159, compared with β = 0.165 for the population-level effect (a prediction ratio of 96%; Fig. 4b and Supplementary Tables 35 and 36). 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 behavioural traits, such as educational attainment (mean within/population predictive ratio of around 60%)[4,5,53], cognitive ability (around 80%)[4,5] and externalizing psychopathology (about 75%)[22].

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 another[52]. We used 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 population-level PGI prediction (Fig. 4 and Supplementary Table 44), indicating that genetic associations with personality operated nearly exclusively through direct transmission from parent to offspring. The identicality of these results to those of within-twin PGI analyses indicates negligible confounding from effects that siblings have on one another. Only for conscientiousness, non-transmitted genetic confounds were significantly predictive of offspring personality (explaining 8.1% of the total predicted effect, indirect effect B = 0.015, 95% CI = 0.003–0.027, P = 0.01). Non-transmitted confounds did not differ in magnitude across mothers and fathers (Supplementary Table 45). By contrast, for educational attainment, only 75.1% of variance was explained by direct effects (indirect effect B = 0.069, 95% CI = 0.055–0.083, $P = 3.3 \times 10^{-21}$; Supplementary Table 44). After controlling for familial confounds, PGI prediction of extraversion by the extraversion PGI (B = 0.207) was similar in magnitude to PGI prediction of educational attainment by the educational attainment PGI[53] (B = 0.208). 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-practice quality control[5]. For neuroticism, we combined these data with published within-family GWAS estimates (Supplementary Table 46 and Extended Data Fig. 10).

LDSC-estimated h^2_{SNP} values from within-family GWAS ranged from 7.6% (s.e. = 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 (Fig. 4 and Supplementary Table 47). 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 (Fig. 4). For each trait, LDSC within-family intercepts were lower than population-level intercepts, suggesting that these models accounted for residual confounding in population-level models.

h^2_{SNP} comparisons across models, using $P < 0.05$ as a significance threshold to maximize identification of potential differences, indicated that, for only openness to experience, matched population-level h^2_{SNP} estimates were significantly greater than within-family h^2_{SNP} estimates (19.4%, 95% CI = 15.8–22.9% versus 13.4%, 95% CI = 7.1–19.6%, P = 0.02). 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 46). By contrast, previously reported comparisons for other social and behavioural traits, such as educational attainment, depression and household income, indicate that LDSC h^2_{SNP} is attenuated by up to 50% in within-family data[5]. LDSC-estimated genetic correlations between within-family and population-level GWAS summary data averaged r_g = 0.86 and were significantly less than 1.00 only for neuroticism (r_g = 0.75, 95% CI = 0.61–0.90, $P < 0.001$) and agreeableness (r_g = 0.79, 95% CI = 0.61–0.97, P = 0.03). These results indicate strong correspondence in genetic effect estimates between population-level and within-family

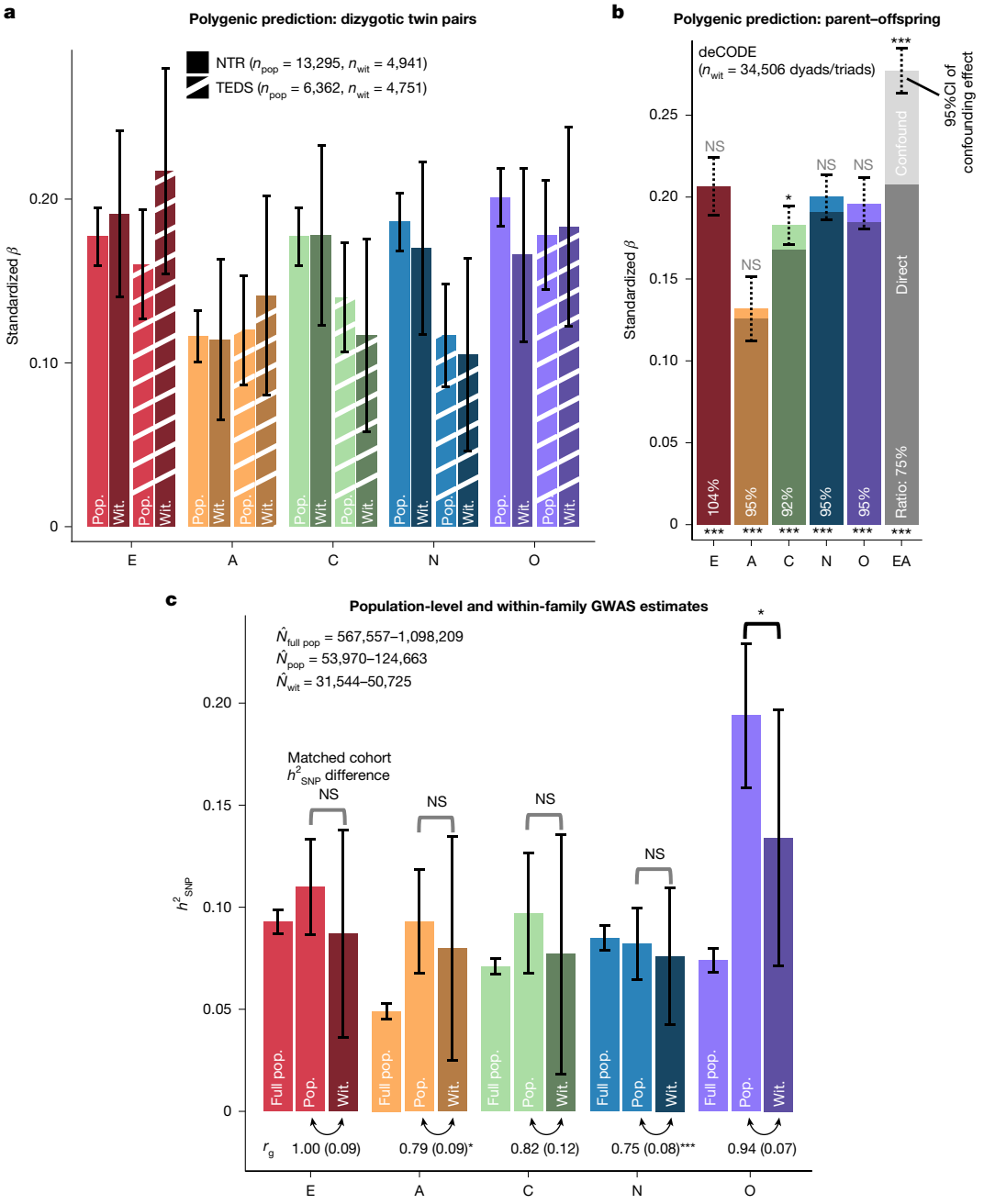

Fig. 4 | Evaluating familial confounding in genetic associations with personality. a, Population-level and within-family PGI prediction in two cohorts: NTR and TEDS. **b**, The total PGI prediction for parent–offspring in the deCODE cohort (significance is indicated by asterisks below the corresponding bar), decomposed into directly transmitted effects (effects of the proband's PGI; darker bars) and familial confounds (effects of the proband's parents' PGIs; lighter bars). The 95% CIs and significance asterisks for estimated familial confounding are shown (Supplementary Table 44). The ratio of direct effects to direct plus confounding effects is shown at the bottom of the corresponding bar. Comparison estimates for educational attainment (EA) come from a PGI constructed from the ref. 53 GWAS of educational attainment with the deCODE and 23&Me cohorts held out. In **a** and **b**, point estimates are standardized β values from regressions predicting phenotypic personality traits using PGI weights derived from the EUR-like population-level GWAS. **c**, h^2_{SNP} estimates were determined using 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 46). The r_g value below each pair of traits indicates their genetic correlation estimated using LDSC, with deviation from $r_g = 1$ tested using a nested χ^2 model in genomic structural equation modelling. The *P* values above each pair of traits indicate the results of a test for differences in h^2_{SNP} between population and within-family estimates. For **a**–**c**, the error bars depict the 95% CIs and standard errors are shown in parentheses. *P* values were calculated using two-sided tests with no correction for multiple testing. NS, not significant ($P \geq 0.05$); *$P < 0.05$, ***$P < 0.001$.

analyses, but we note generally wider CIs, 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 similar 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 and Supplementary Table 47).

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 = 0.83; Supplementary Table 48 and Extended Data Fig. 10). Fully within-family genetic correlations between these summary data and 18 phenotypes from ref. 4 were also highly similar to population-level genetic correlations, despite notably less power (mean r between r_g estimates = 0.87; Supplementary Table 49 and Extended Data Fig. 10).

Discussion

In a consortium effort assembling data from 46 cohorts covering 611,037 to 1.14 million 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[23,45,46]. 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 trade-off between reliability (longer tests) and larger samples that should factor into future data collection. Notably, our h^2_{SNP} estimates, which index only effects of common genetic variants, are markedly lower than the 40–60% heritability estimates produced based on twin and family methods[18,23] 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 effects[51]. This result contrasts with those obtained for other social science traits, such as educational attainment, income, externalizing behaviour and cognitive performance[4,5,22,51,53], 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 people[54], and may interact with and operate through environmental experiences[45].

Genetic associations with personality largely generalized across different regions of Western geography, age groups, self-rated versus other-rated report, military service versus 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, analyses stratified by sex, more finely by age, and by more expansive sets of 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 personality traits occur through 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 pre-existing 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 aetiology.

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, labour market performance and reproduction, as well as specific behaviours such as 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 time[26] and resistant to simple experimental manipulation[49]. 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 content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-026-10992-9.

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Methods

Cohorts and measures

We incorporated personality trait data from 46 cohorts participating in the 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 1 and 2. Descriptions of each cohort are provided in Supplementary Note 7. A PRISMA flowchart for this meta-analysis is available at OSF (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 of the 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 genomes[56] 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 < 0.40) 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 mislabelled demographic data[57]) 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 SNP[58] with PLINK2 (ref. 59), PLINK[60], GCTA[61], BOLT-LLM[62], FastGWA[63] or proprietary software, using mixed models to account for relatedness when appropriate. These analyses included controls for age, age^2, 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-analysed estimates while accounting for dependency of their estimation errors. We harmonized and directionally aligned effects using EasyQC[64] and checked that effects were directionally consistent across cohorts by estimating genetic correlations with LDSC[34] (conducted on HapMap3 SNPs with an INFO threshold of ≥0.90) in GenomicSEM[37].

For each Big Five trait, we then conducted IVW meta-analysis of GWAS estimates across all of the contributing cohorts, separately for participants with EUR-like and AFR-like genomes, in R (v.4.3.1)[65]. For each meta-analysed SNP, we re-estimated n using observed meta-analytic MAF and standard error. This produced 10 sets of summary statistics (five traits × two ancestral groups). We quantified the number of genome-wide significant lead SNPs at $P < 5 \times 10^{-8}$ that were linkage disequilibrium (LD)-independent of other lead SNPs nearby on the genome (within a 250 kb window) using FUMA[66]. 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 Fig. 1.

We next 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. As around 95% of participants were of EUR-like ancestry, and because stronger linkage disequilibrium among EUR-like compared with AFR-like superpopulations[67] means that using the EUR reference panel probably 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 MAMA[31].

We tested the consistency of the 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 250 kb 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 250 kb 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. As 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 regression[68], and we estimated within-trait transancestry genetic correlations using POPCORN[69].

We additionally applied LDSC to GWAS data on each individual cohort and then meta-analysed h^2_{SNP} estimates across cohorts using fixed-effects and random-effects meta-analyses, with the R package metafor[70]. 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 α reliability of its personality measure (reliabilities are shown 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: geographical region (US, UK–Australia, continental Europe and Nordic), age group (most participants <25 years, 25–64 years and 65 years and older), 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[71–74], NEO Personality Inventory[75–79], International Personality Item Pool inventories[80,81], 100 Nuances of Personality Inventory[82] and Eysenck Personality Inventory[83,84]). We next estimated genetic correlations across groups using bivariate LDSC. Finally, we compared X-chromosomal associations with neuroticism across male and female individuals in the UK Biobank cohort, estimating h^2_{SNP}, cross-sex r_g and the dosage compensation ratio[85,86] on sex-stratified summary data of unrelated male ($n = 168{,}856$) and female ($n = 197{,}927$) individuals 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 model[87]. 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 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 MAGMA[88], including SNPs with INFO ≥ 0.80. The gene sets included in this analysis came from previous work[89]. 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 PGI weights for each Big Five trait by applying SBayesR[42] 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, age^2, sex, 10 ancestral principal components and genotyping batch effects, with significance set at $P < 0.01$. We also generated PGI weights both among a broader set of 2.9 million SNPs and, using PRS-CSx[90], we compared this prediction to prior estimates. As we describe further in Supplementary Note 4, these changes did not improve prediction, so we focus on analyses using SBayesR and the set of 1.3 million HapMap SNPs.

Associations with behaviours 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 $P < 0.01$ 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 behaviours and outcomes that have not been submitted to GWAS and could therefore not be analysed with LDSC. To do this, we adapted the method described in the 'Polygenic prediction of personality' section above to predict each behaviour or 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 five principal components. We further filtered results to only those that directionally replicated within family to reduce potential confounding (see the 'Evaluating familial confounding' section below) and applied the false-discovery rate correction[91].

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 the 'Population-level meta-analysis' section above). We then estimated a structural equation model in the R package lavaan[92] that used the two PGIs as indicators of a latent, measurement error-free PGI for each participant[36]. We correlated these PGIs across pairs of spouses, siblings and cousins in the UK Biobank and deCODE cohorts (a path diagram of this latent correlation model is provided in Extended Data Fig. 8b). 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 MR analyses to examine putatively causal bidirectional effects between personality traits and external phenotypes, using the R package TwoSampleMR[93]. For these tests, we selected 13 external behaviours 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 assumptions[94]: weighted mode with Steiger filtering[95] weighted median with Steiger filtering[96] and MR-CAUSE[97]. 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 or 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 age^2. 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, age^2 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 according to the procedure used for the Big Five, using GWAS summary data from a previous study[53], excluding 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 snipar[30] or a pipeline developed previously[4]. For these analyses, we conducted stringent quality control, including only SNPs with imputation INFO ≥ 0.99 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 data[4]. 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 the 'Population-level meta-analysis' section above, restricted to SNPs with INFO ≥ 0.99 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 intercepts[34]. We used nested model comparison tests in genomic structural equation modelling 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 unity[98]. 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 >250 kb 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 behaviours or outcomes. We compared these correlations to the corresponding estimates fully based on population-level GWAS. We also estimated genetic correlations entirely based on within-family GWAS (for which summary data were available for 18 external behaviours or outcomes)[4]; these estimates were compared with the corresponding estimates based completely on population-level GWAS.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Summary statistics for GWAS of each Big Five trait, excluding 23andMe participants, are available at OSF[99] (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 split-half 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, on request.

Code availability

Code for all analyses performed this study is available at OSF[99] (https://doi.org/10.17605/OSF.IO/HGNSM).

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Author contributions T.S., M.L.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.L.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 Á.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. Võsa, L.A., A.R., M.V., J.A., T. Esko, R.M., U. Vainik, G.A.J., G.T., Á.F.G., G.B., T.E.T., H. Stefansson, K. Stefansson, R.C., Q.Q., E.C.C., H.A., F.A.T., E.Y., M.T., D.I.B., E.J.C.d.G., 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. Silventoinen, T.P., A.M., K. Rimfeld, R. Plomin, M. Malanchini, D.M.D., F.A., L.W.W., F.U., M.A.M., H.R.K., Y.N., S.B., R. Polimanti, T. Edwards, A.G., E.A.W., J.J.L., M. McGue., A. Terracciano, M. Marongiu, E.F., F.C., A.R.S., P.J.v.d.M., 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. Räikkönen, J.G.E., J.L., G.D., P.R., A. Taylor, 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.d.l.F. developed software used in the study. W.A.A., P.T.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.v.d.M., C.X., M.L., I.J.D., W.D.H., H.D., F.S., L.F. and 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 of the authors approved the final version of the manuscript.

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Additional information

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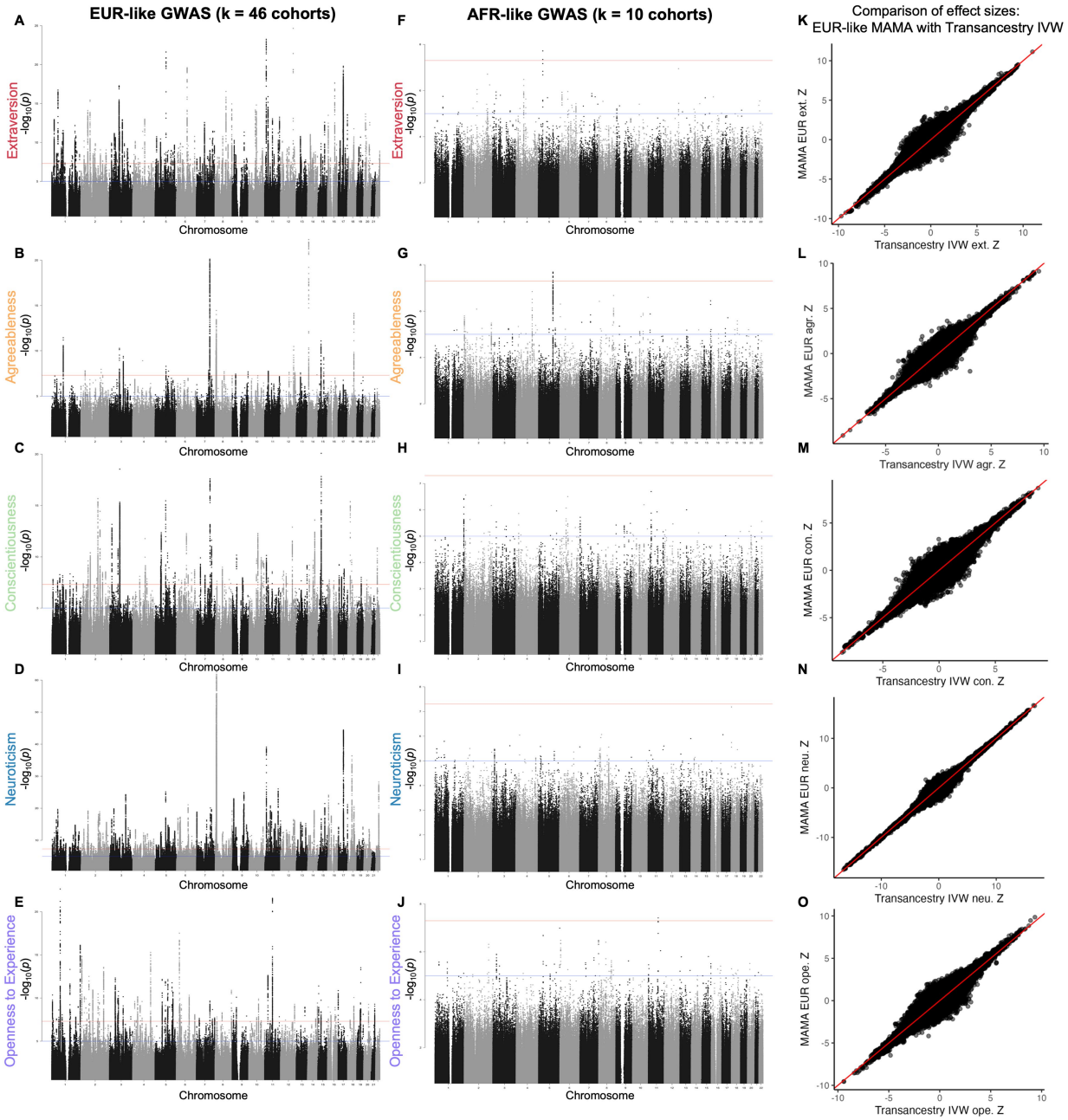
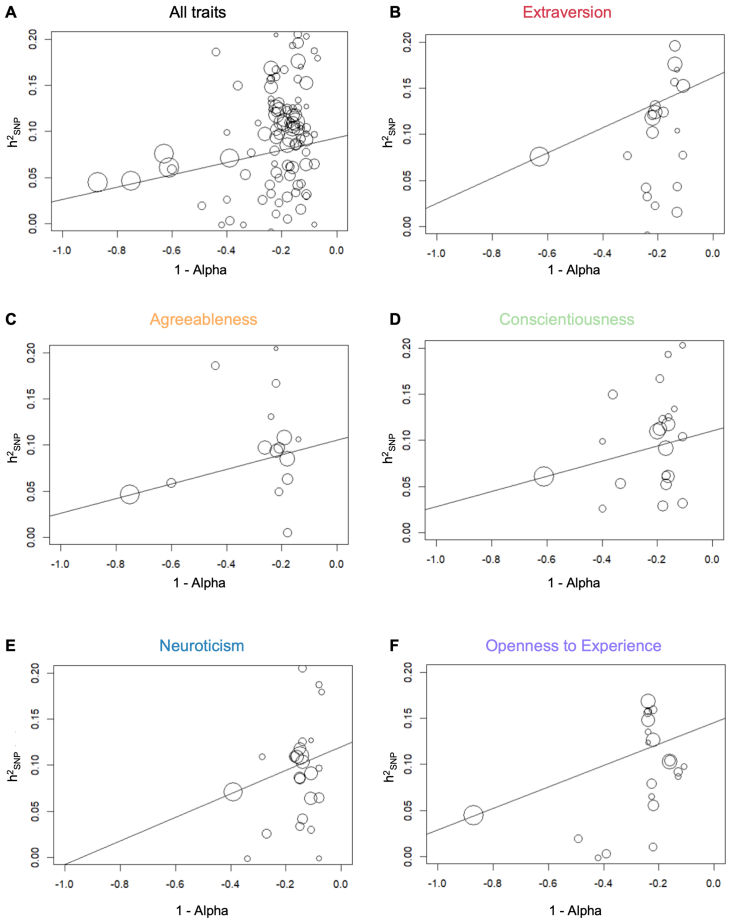
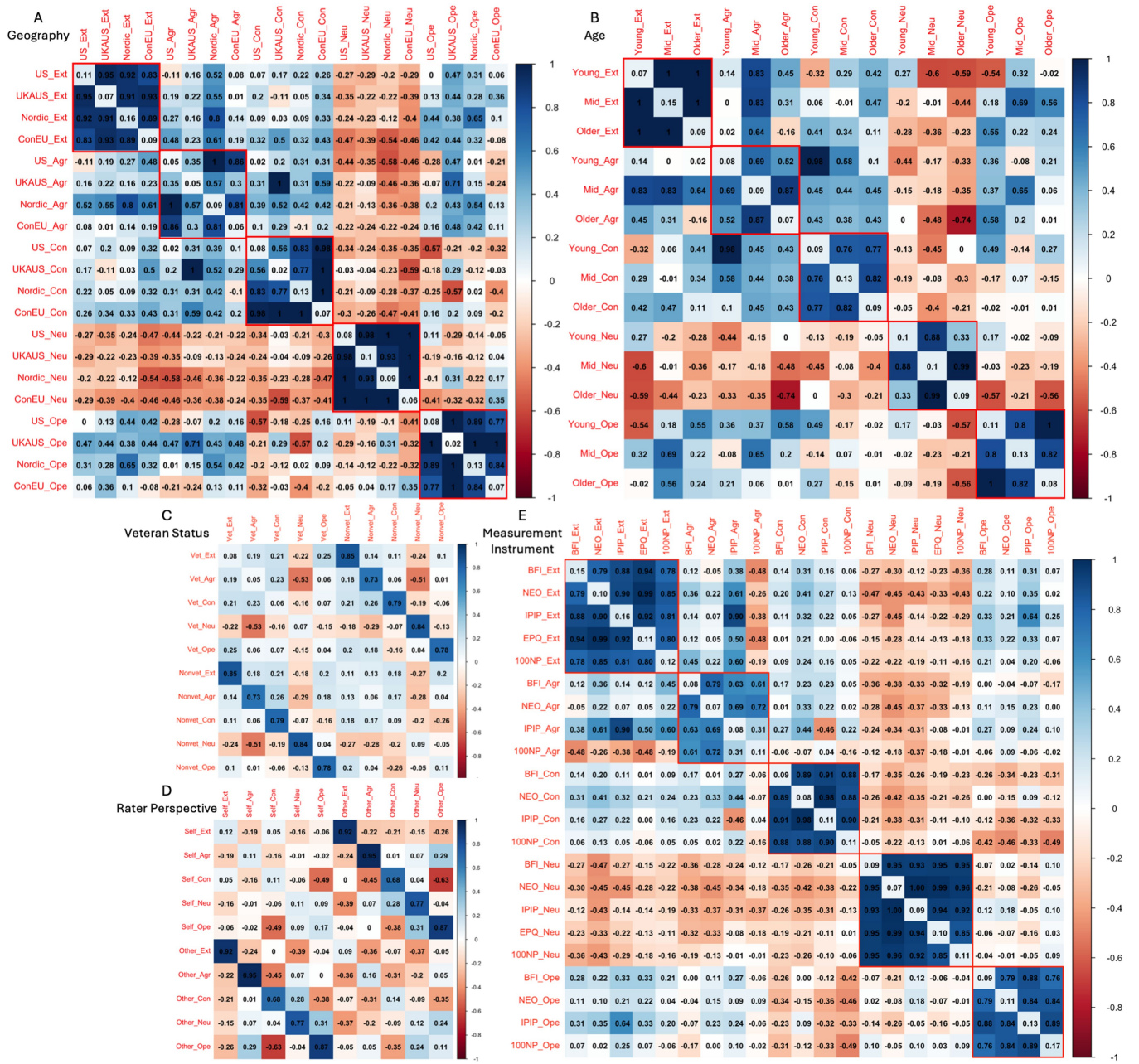


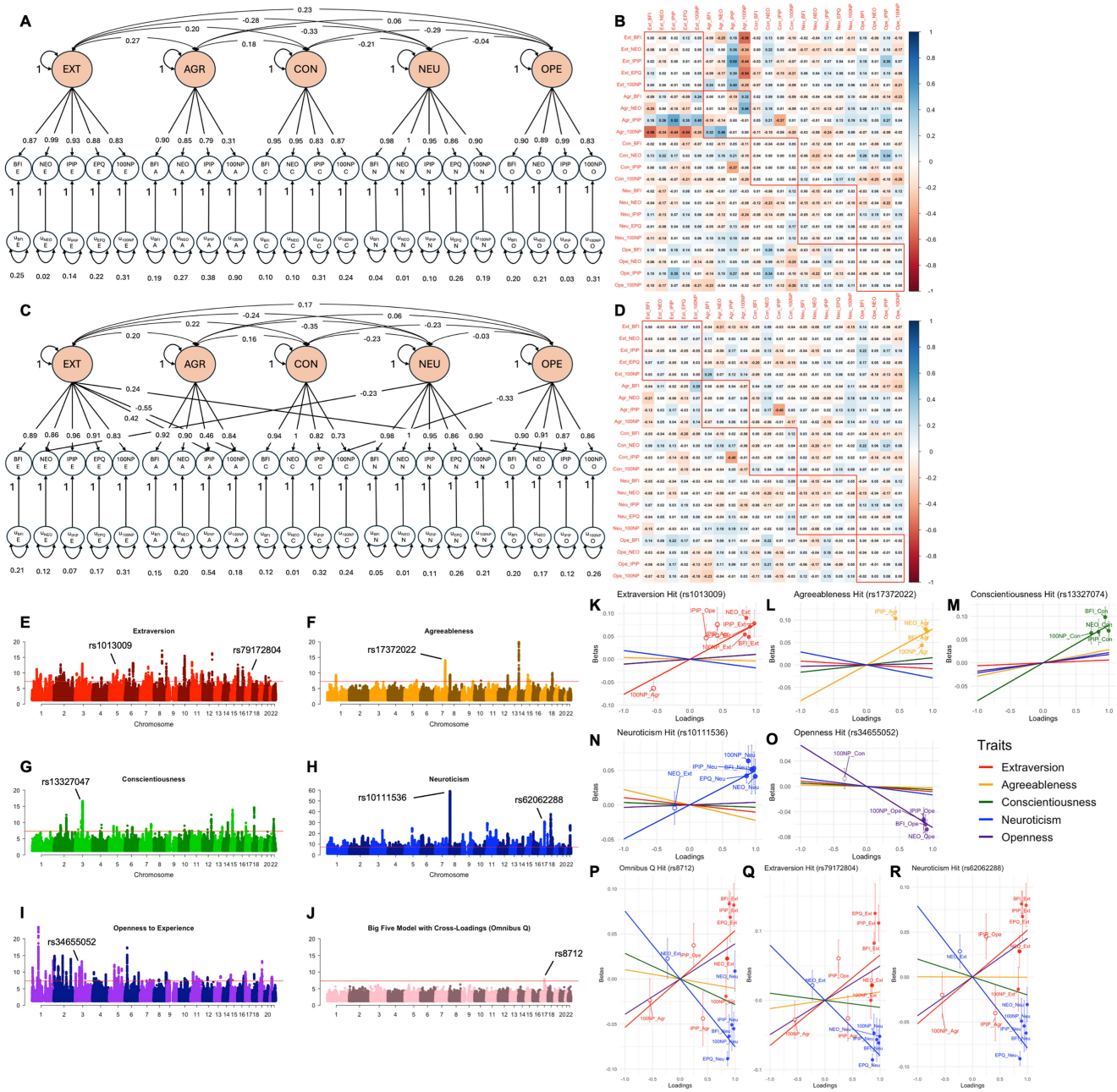
Extended Data Fig. 1 | Visualization of ancestry-specific meta-analyses. **Panels A-E** depict Manhattan plots among meta-analysed cohorts of participants with EUR-like genomes for the traits of Extraversion (N = 620,193), agreeableness (N = 567,556), conscientiousness (N = 598,047), neuroticism (N = 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-analysed 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 Fig. 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.

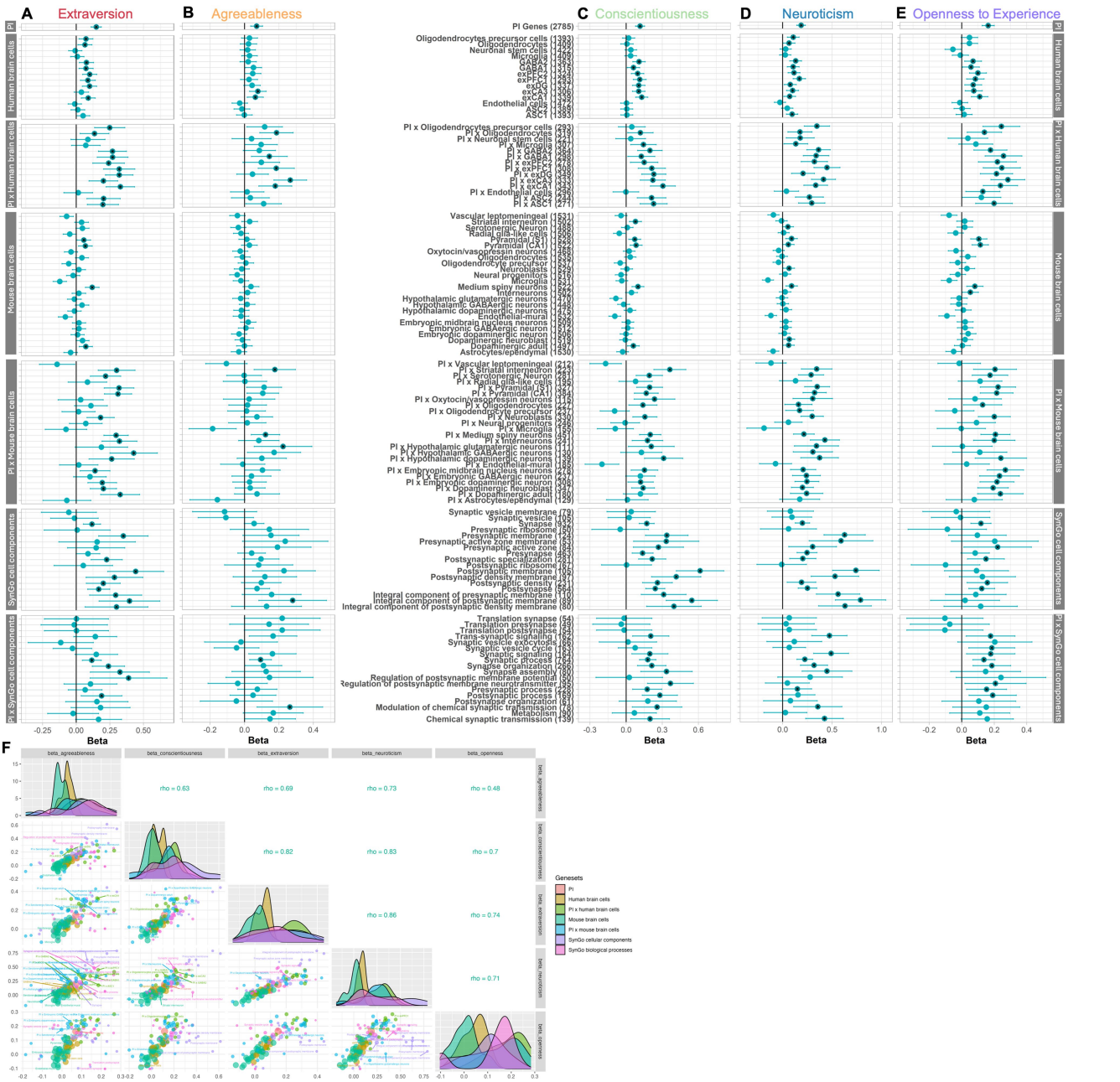


Extended Data Fig. 3 | LDSC Genetic correlations stratified by groups: geographic regions, age groups, veteran status, rater perspective, and measurement instrument. Panel A depicts associations between and among four geographic regions: US = United States. UKAUS = United Kingdom and Australia. ConEU = 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 ±1.5 SD ≤ 25. Mid = Mean cohort age ±1.5 SD = 26–64. Older = Mean cohort age ±1.5 SD ≥ 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 trait measured by each questionnaire is presented on the diagonal. Red squares denote genetic correlations among measures of the same trait across questionnaires.

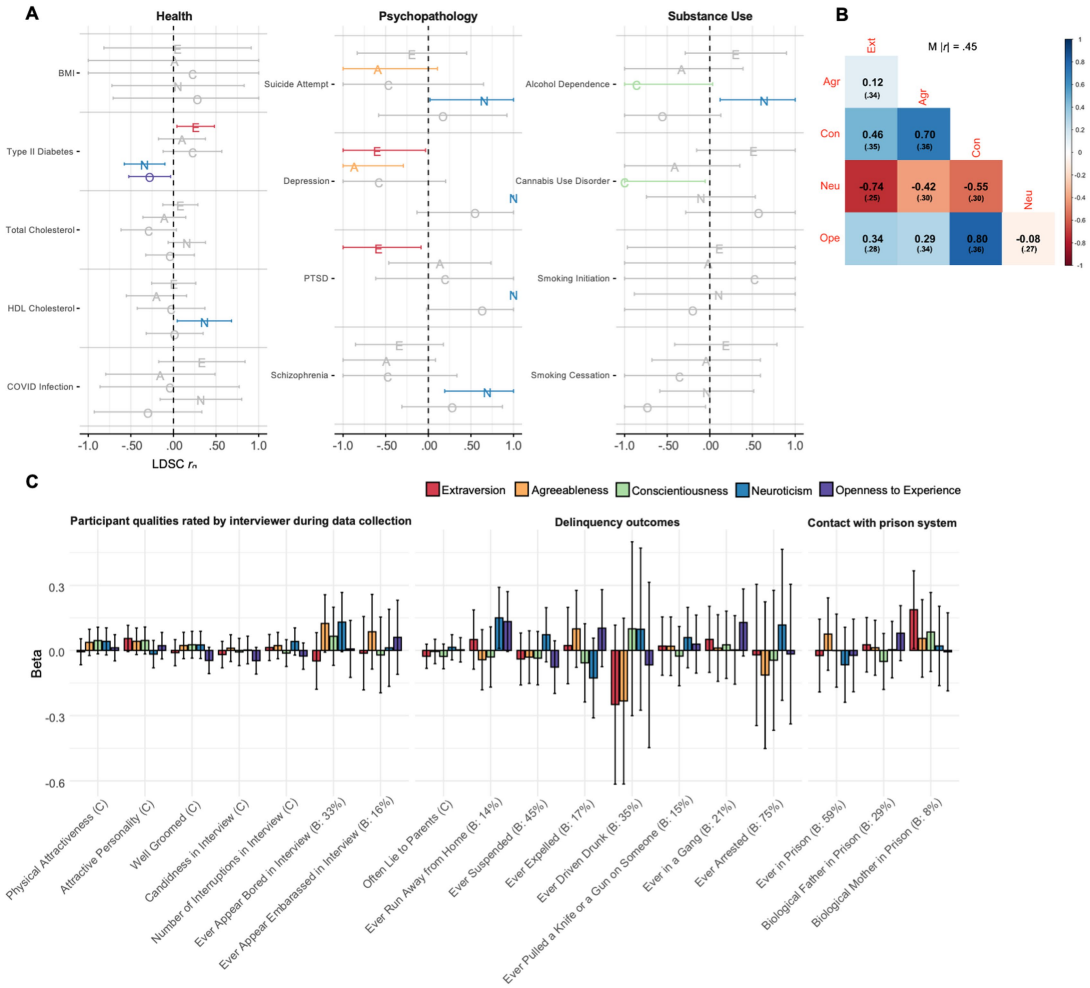


Extended Data Fig. 4 | See next page for caption.

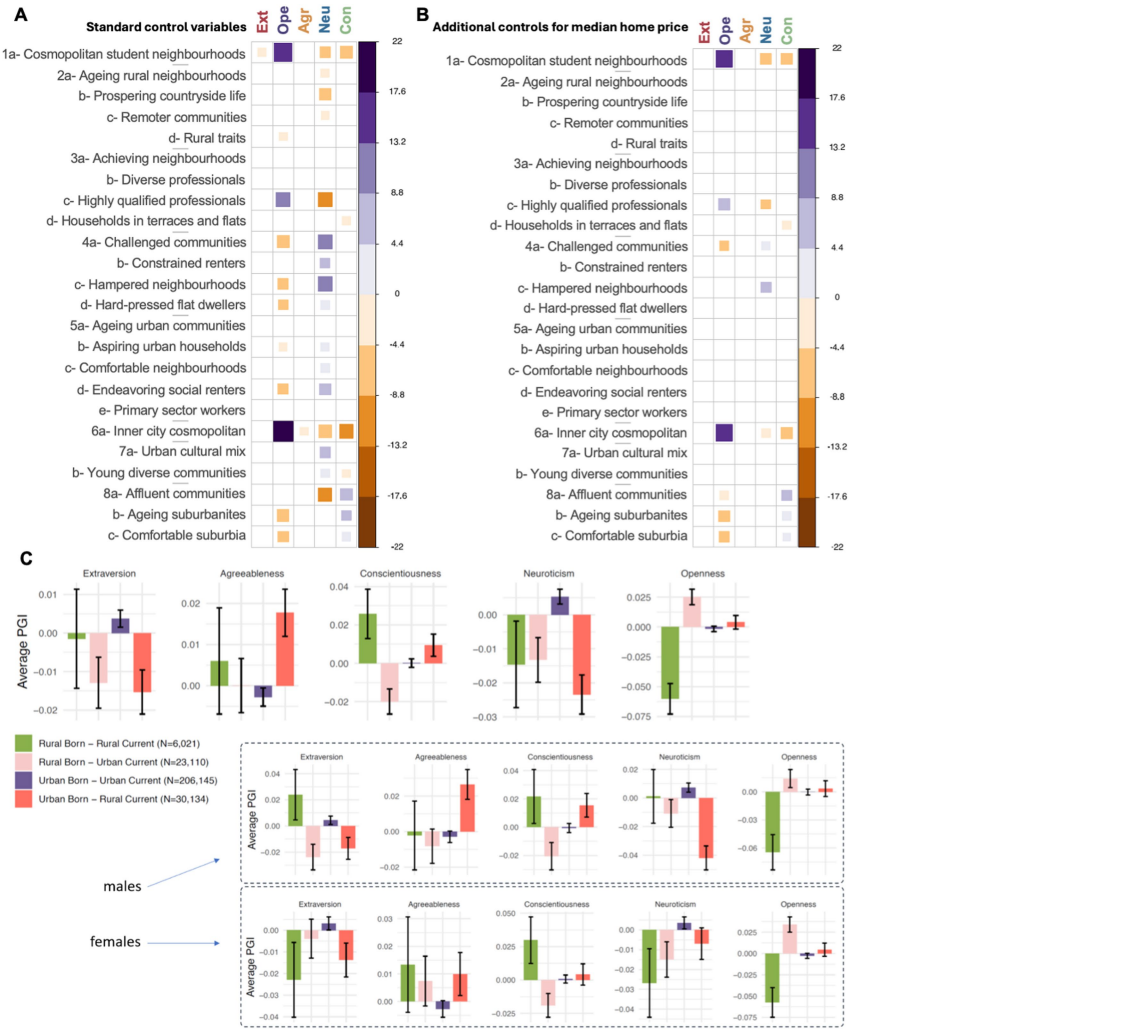
Extended Data Fig. 4 | Multivariate analysis of genetic signal across measurement instruments. Panel A depicts a confirmatory five-factor model of measurement-instrument stratified GWAS of the Big Five, conforming to simple structure. Standardized estimates are displayed. BFI = Big Five Inventory. IPIP = 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 coloured 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 coloured 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.



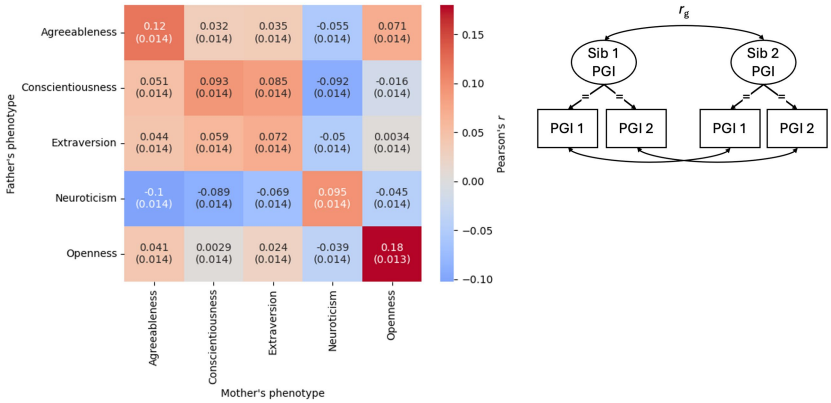
Extended Data Fig. 5 | Gene-set heritability enrichment analyses. **Panels A-E** depict enrichment for each of the Big Five traits. Each point estimate depicts the standardized enrichment beta; bars correspond to standard errors. PI = Protein-Truncating Intolerant genes. An X indicates the intersection 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[91]. **Panel F** depicts pairwise rank correlations of enrichment betas across the Big Five. 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.



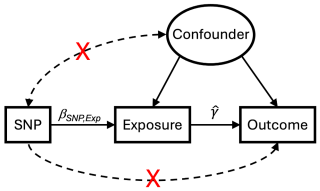
Extended Data Fig. 6 | Genetic correlations and PGI associations among participants with AFR-like genomes. Panel A depicts Genetic correlations between personality and health, psychopathology, and substance use, estimated using LDSC. Letters correspond to point estimates of genetic correlation,. Note. E = Extraversion. A = Agreeableness. C = Conscientiousness. N = Neuroticism. O = Openness to Experience. Error bars depict 95% confidence intervals. Associations not significant with two-sided test $p < 0.05$, with no further correction for multiple testing, are depicted in grey. 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 using polygenic index weights derived from the EUR-like GWAS applied to participants with AFR-like genomes (N = 1,753). Note: Point estimates for effect sizes of continuous outcomes (labelled with a parenthesized C) are in standardized units, whereas associations with binary outcomes (labelled with a parenthesized 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 $p < 0.05$, with no further correction for multiple testing. Full numeric results are provided in Supplementary Table S39.



Extended Data Fig. 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 Middle-layer Super Output Area geographic 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 standardized units. Error bars represent 95% confidence intervals.

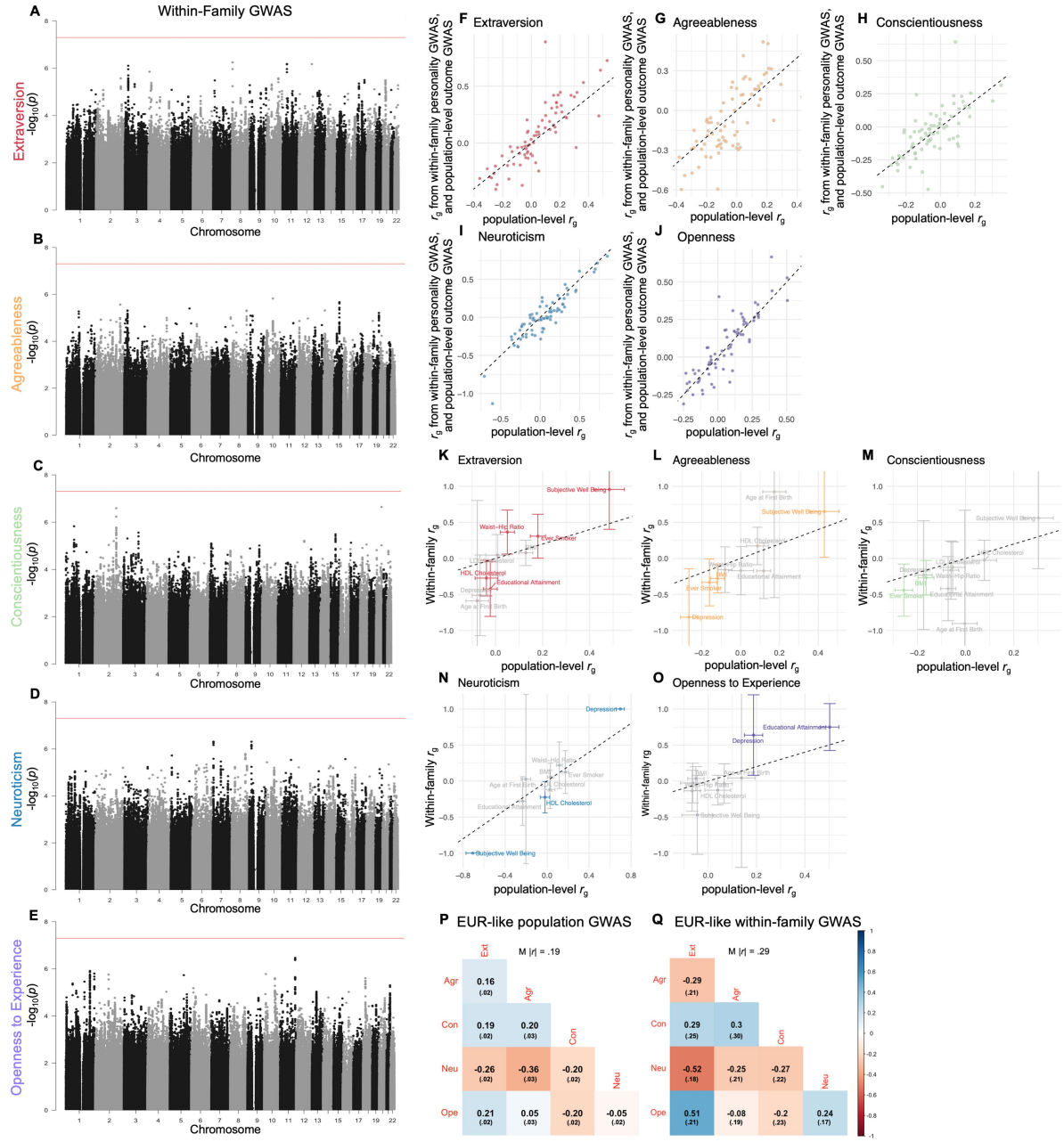


Extended Data Fig. 8 | Assortative Mating. The left side of the figure depicts phenotypic correlations between mothers and fathers in the deCODE cohort (N = 5,317 unique mate pairs). Mates were defined as individuals known to have children together in the deCODE genealogical database. Each square shows the correlation coefficient with standard error in parenthesis. See also Supplementary Tables S40. The right side of the figure 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 Fig. 9 | Mendelian Randomization. The figure on top 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. The table 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 Fig. 10 | Within-Family GWAS results. Panels A-E depict Manhattan plots among meta-analysed 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 Fig. 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 Fig. 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 coloured if the within-family genetic correlation is significant at $p < 0.05$ and grey 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.

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Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

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☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
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☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☐	☒ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Analyses were conducted using the Howe and colleagues (2022) within-sibship analytic pipeline, the programs fastGWA (Jiang et al., 2019), PLINK version 1.9 (Purcell et al., 2007), PLINK2 (Chang et al., 2015), GCTA version 1.94 (Yang et al., 2011), BOLT-LMM version 2.4.1 (Loh et al., 2015),FUMA (Watanabe et al., 2017) POPCORN (Brown et al., 2016), MAGMA (de Leeuw et al., 2015), PRS-CSx (Ruan et al., 2022), SBayesR (Lloyd-Jones et al., 2019), SNiPAR (Young et al., 2022), SLD4M (O'Connor et al., 2019), and R version 4.3.1 (R Core Team, 2023) using R data-management packages dplyr (Wickham et al., 2019), data.table (Dowle et al., 2019), and psych (Revelle, 2017), R visualization packages corrplot (Wei et al., 2017), ggplot2 (Wickham et al., 2019), and qqman (Turner, 2014), and R analysis packages lavaan (Rosseel, 2012), lme4 (Bates, 2010), metafor (Viechtbauer, 2010), EasyQC (Winkler et al., 2014), GenomicSEM (Grotzinger et al., 2019), and ieugwasr and TwoSampleMR (Hemani et al., 2018).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

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, AFR, and trans-ancestry meta-analytic population-level summary statistics, polygenic index weights, and EUR 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

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	In this study, chromosomal sex was coded for each participant and used as a control variable in polygenic index analyses, following field-standard procedures, as well as a stratifying variable in some X-chromosomal analyses, when noted.
Reporting on race, ethnicity, or other socially relevant groupings	Some analyses require the stratification of participants by recent genetic ancestry. To refer to ancestry groups while minimizing potential stigma, we follow guidance from National Academy of Sciences (https://nap.nationalacademies.org/read/26902/chapter/9) and use broad, overarching terms like EUR and AFR, or European-like and African-like genomes. Specifically, the term EUR/AFR refers to participants whose genomes are most similar to the participants in the 1000 Genomes European/African superpopulation sample (https://www.internationalgenome.org/).
Population characteristics	Demographic characteristics of each of the 46 cohorts, including sample size, age, and site of geographical ascertainment are described in full in the supplementary text and supplementary tables 1 and 2.
Recruitment	Recruitment was handled per-cohort, each using different procedures. Full information is contained in the supplementary text.
Ethics oversight	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 the Supplementary Text. All participants consented to the research, and this research was performed in accordance with all relevant guidelines and regulations.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	This is a genome-wide association study using quantiative genomic and personality trait dat
Research sample	The sample for this study is a meta-analysis of 46 different study cohorts who are members of the Revived Genomics of Personality Consortium. Sample size, demographic information, and sampling strategy differs by cohort. See supplementary text for complete information.
Sampling strategy	Sampling strategy varied by cohort; full information on sampling is provided in the cohort information at the end of the supplementary note. Most cohorts were not representative of their respective populations and were convenience samples or samples designed to collect data on twin sibling dyads. No pre-determined sample size was calculated; analyses make use of all available data to maximize power.
Data collection	Data collection varies by cohort; full information on data collection is provided in the cohort information at the end of the supplementary note. Each cohort collected a genomic sample and measured the Big Five personality traits using a valid questionnaire. There was no blinding nor randomization, as participants were not stratified into conditions.
Timing	No primary data was collected for this study. Start and stop of data collection varies by cohort. See supplementary text for complete information for each cohort
Data exclusions	Genotypes were aligned to build 37/hg19 on the forward strand, excluding SNPs with Minor Allele Frequency (MAF) < 1%, Call rate <95%, those that deviated from Hardy-Weinberg Equilibrium ($p < 1x10-6$), and those with poor clustering on visual inspection of intensity plots. SNPs were excluded per analysis if they were below a minimum effective sample size threshold (e.g., 5,000). Participants were excluded prior to cohort-level analysis if they had low overall call rates (< 95%), excess autosomal heterozygosity or homozygosity, were duplicate samples, had sex inconsistent with gender, or had chromosomomal abnormalities. As such exclusion rate cannot be calculated at the meta-analytic level.

Non-participation	Non-participation varies by cohort and was handled on a per-cohort basis.
Randomization	There was no randomization to condition in this study. Genome-wide analyses included controls for age, age2, birth cohort, sex, and genetic principal components, to address potential lifespan and birth cohort differences in personality traits. Within-family analyses included controls for genomes of family members to reduce confounding due to shared environment.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	*Report on the source of all seed stocks or other plant material used. If applicable, state the seed stock centre and catalogue number. If plant specimens were collected from the field, describe the collection location, date and sampling procedures.*
Novel plant genotypes	*Describe the methods by which all novel plant genotypes were produced. This includes those generated by transgenic approaches, gene editing, chemical/radiation-based mutagenesis and hybridization. For transgenic lines, describe the transformation method, the number of independent lines analyzed and the generation upon which experiments were performed. For gene-edited lines, describe the editor used, the endogenous sequence targeted for editing, the targeting guide RNA sequence (if applicable) and how the editor was applied.*
Authentication	*Describe any authentication procedures for each seed stock used or novel genotype generated. Describe any experiments used to assess the effect of a mutation and, where applicable, how potential secondary effects (e.g. second site T-DNA insertions, mosiacism, off-target gene editing) were examined.*