

Life Sciences Reporting Summary

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► Experimental design

1. Sample size

Describe how sample size was determined.

We made use of data collected by external sources (UK biobank, 23andMe, Genetics of Personality Consortium and the Psychiatric genetics Consortium). For all samples the sample size consists of all individuals that remain after quality control of the data and exclusion of withdrawn subjects. Detailed information on the samples used, as well as the exclusion/inclusion criteria, are provided in the Online Methods (sections: Samples, Genotyping and imputation, Genome-wide association analyses).

2. Data exclusions

Describe any data exclusions.

See Online Methods.
For UKB data: we excluded participants from further analyses if they had excessive missing phenotypic data (section: Phenotype assessment), did not pass standard quality control or withdrew their consent to participate in the UK biobank study (section: Genotyping and imputation).

3. Replication

Describe whether the experimental findings were reliably reproduced.

We used a meta-analytic approach, which inherently evaluates the combined evidence for significant association across samples. In addition, we used polygenic risk score profiling to determine whether our current results were predictive of the same outcome in three independent samples.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

NA

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

NA

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a Confirmed

- ☐ ☒ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
- ☐ ☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☒ ☐ A statement indicating how many times each experiment was replicated
- ☐ ☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
- ☐ ☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
- ☐ ☒ The test results (e.g. P values) given as exact values whenever possible and with confidence intervals noted
- ☐ ☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
- ☐ ☒ Clearly defined error bars

See the web collection on [statistics for biologists](#) for further resources and guidance.

► Software

Policy information about [availability of computer code](#)

7. Software

Describe the software used to analyze the data in this study.

Standard statistical genetics software packages were used for the analyses described in the current manuscript (all are described in more detail in the Online Methods). Below we list the software used:
 Plink - Open-source software (Purcell et al., 2007; Chang et al., 2015) used to conduct genome-wide association analyses.
 MAGMA - In-house developed software (de Leeuw et al., 2015) for performing gene-based analyses.
 FUMA - In-house developed online platform for functional annotation of GWAS results (Watanabe et al., 2017)
 LD Score Regression - Used to compute SNP-based heritability and genetic correlations (Bulik-Sullivan et al., 2015)
 PRSice - Polygenic Risk Score analysis (Euesden et al., 2015)
 LDpred - Polygenic Risk Score analysis (Vilhjálmsdóttir et al., 2015)
 GSNR - Generalized Summary-based Mendelian Randomization (Zhu, Z. et al. 2018)

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* [guidance for providing algorithms and software for publication](#) provides further information on this topic.

► Materials and reagents

Policy information about [availability of materials](#)

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.

Summary statistics from our neuroticism meta-analysis, our depression meta-analysis, and the GWA analyses for depressed affect and worry will be made available for download at <https://ctg.cncr.nl/>. Note that our freely available meta-analytic sumstats concern results excluding the 23andMe sample. This is a non-negotiable clause in the 23andMe data transfer agreement, intended to protect the privacy of the 23andMe research participants.

23andMe participant data are shared according to community standards that have been developed to protect against breaches of privacy. Currently, these standards allow for the sharing of summary statistics for at most 10,000 SNPs. The full set of summary statistics can be made available to qualified investigators who enter into an agreement with 23andMe that protects participant confidentiality. Interested investigators should contact David Hinds (dhinds@23andme.com) for more information.

Neuroticism summary statistics from the Genetics of Personality Consortium (GPC1) are freely available for download at: <http://www.tweelingenregister.org/GPC/>

Depression summary statistics from the Psychiatric Genetics Consortium (PGC) are freely available for download at: https://www.nimhgenetics.org/available_data/data_biosamples/pgc_public.php

For further information, see Online Methods, section Data Availability.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).

No antibodies were used.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

No eukaryotic cell lines were used.

b. Describe the method of cell line authentication used.

No eukaryotic cell lines were used.

c. Report whether the cell lines were tested for mycoplasma contamination.

No eukaryotic cell lines were used.

d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by [ICLAC](#), provide a scientific rationale for their use.

No commonly misidentified cell lines were used.

► Animals and human research participants

Policy information about [studies involving animals](#); when reporting animal research, follow the [ARRIVE guidelines](#)

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.

No animals were used in this study.

Policy information about [studies involving human research participants](#)

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.

We utilized data collected previously by external sources. All individuals included in the study provided informed consent, and all original studies were approved by the concerned ethical committee (see Online Methods; section 'Samples')