

## Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see [Authors & Referees](#) and the [Editorial Policy Checklist](#).

### Statistics

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

n/a Confirmed

- ☐ ☒ The exact sample size ( $n$ ) for each experimental group/condition, given as a discrete number and unit of measurement
- ☐ ☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
- ☐ ☒ 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

Qualtrics was used to collect survey data. GenomeStudio was to generate genotype data.

Data analysis

PRSice V2 was used to calculate MDD polygenic risk score. The statistic analysis was conducted by R (v3.4.4, packages: base packages, lme4, mediation, ggplot2) and SAS (v9.4, PROC GLIMMIX).

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/reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research [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 list of figures that have associated raw data
- A description of any restrictions on data availability

The de-identified data from Intern Health Study is available through the Psychiatric Genomics Consortium (PGC): <https://www.med.unc.edu/pgc/shared-methods>.

## Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

- ☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

## Life sciences study design

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

|                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Sample size     | The prediction power and accuracy of polygenic risk score study is mostly dependent on the discovery sample. In this paper, the discovery sample is from PGC, UKB and 23andMe, and the sample size (246,363 cases and 561,190 controls) is the biggest for publicly major depression disorder GWAS so far.<br>The sample size of 5,227 in the target sample (i.e. interns in our study) is sufficient achieve meaningful results in polygenic risk score study. Reference: Marees, A. T. et al. A tutorial on conducting genome-wide association studies: Quality control and statistical analysis. Int. J. Methods Psychiatr. Res. 27, e1608 (2018). |
| Data exclusions | Subjects was excluded when: no sufficient survey data, duplicated or low quality genotype data. The inclusion criteria of survey data followed previous publications from Intern Health Study. The quality check process of genotype data followed well-established and published protocols.                                                                                                                                                                                                                                                                                                                                                          |
| Replication     | Replications were done: 1) in 5,116 subjects who fit a more conservative definition of European ancestry, and obtained fundamentally unchanged results; 2) using MDD-PRS generated with eight less inclusive p-value thresholds, the associations and interactions remained significant; 3) with imputed data derived MDD-PRS, and the results were slightly attenuated but still significant; 4) in East Asian and South Asian groups, and failed to produce significant results due to cross-ethnicity discrepancy in polygenic risk score prediction and smaller sample size.                                                                      |
| Randomization   | Randomization is not relevant to our study as there's no group allocation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Blinding        | Blinding is not relevant to our study as there's no group allocation.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

## 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.

| Materials & experimental systems    |                                                                 | Methods                             |                                                 |
|-------------------------------------|-----------------------------------------------------------------|-------------------------------------|-------------------------------------------------|
| n/a                                 | Involved in the study                                           | n/a                                 | Involved in the study                           |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Antibodies                             | <input checked="" type="checkbox"/> | <input type="checkbox"/> ChIP-seq               |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Eukaryotic cell lines                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> Flow cytometry         |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Palaeontology                          | <input checked="" type="checkbox"/> | <input type="checkbox"/> MRI-based neuroimaging |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Animals and other organisms            |                                     |                                                 |
| <input type="checkbox"/>            | <input checked="" type="checkbox"/> Human research participants |                                     |                                                 |
| <input checked="" type="checkbox"/> | <input type="checkbox"/> Clinical data                          |                                     |                                                 |

## Human research participants

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

|                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population characteristics | The population is first year residents (medial interns) in USA, with average age of 27.6 years old (SD = 2.7yrs), 50.3% females, and of European ancestry.                                                                                                                                                                                                                                                                                          |
| Recruitment                | Interns entering residency programs across specialties in the academic years from 2007 to 2017 were sent an email 2-3 months prior to commencing internship and invited to participate in the study. Subjects consented to participate in the study were given a \$25 gift certificate after completing the baseline survey and another \$25 gift certificate after completing the follow-up survey. There is no bias present to impact the result. |
| Ethics oversight           | The Institutional Review Board at the University of Michigan and the participating hospitals approved the study.                                                                                                                                                                                                                                                                                                                                    |

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