Shared Genomic Architectures of COVID-19 and Antisocial Behavior

Running title: COVID-19 and Antisocial Behavior

Authors
Charleen D. Adams, PhD MPH¹*, Jorim J. Tielbeek, PhD², Brian B. Boutwell, PhD³,4

¹Department of Environmental Health, Program in Molecular and Integrative Physiological Sciences, Harvard T.H. Chan School of Public Health;²Department of Complex Trait Genetics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit Amsterdam, Amsterdam, Netherlands;³School of Applied Sciences, The University of Mississippi;⁴John D. Bower School of Population Health, University of Mississippi Medical Center

Correspondence to:
*Department of Environmental Health, Program in Molecular and Integrative Physiological Sciences, Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115, USA; Tel.: 626-841-3937; Email: cdadams@hsph.harvard.edu.

Word count, manuscript: 1998; word count Abstract: 228

NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
Abstract

Little is known about the genetics of norm violation and aggression (ASB) in relation to coronavirus disease 2019 (COVID-19). To investigate this, we used summary statistics from genome-wide association studies and linkage disequilibrium score regression to calculate a matrix of genetic correlations ($r_{gs}$) for ASB, COVID-19, and various health and behavioral traits. After false-discovery rate correction, ASB was genetically correlated with COVID-19 ($r_g = 0.51; P = 1.54E-02$) and 19 other traits. ASB and COVID-19 were both positively genetically correlated with having a noisy workplace, doing heavy manual labor, chronic obstructive pulmonary disease, and genitourinary diseases. ASB and COVID-19 were both inversely genetically correlated with average income, education years, healthspan, verbal reasoning, lifespan, cheese intake, and being breastfed as a baby. But keep in mind that $r_{gs}$ are not necessarily causal. And, if causal, their prevailing directions of effect (which causes which) are indiscernible from $r_{gs}$ alone. Moreover, the SNP-heritability ($h_g^2$) estimates for both measures of COVID-19 were very low, restricting the overlap of genetic variance in absolute terms between the two traits. Nonetheless, our findings suggest that those with antisocial tendencies possibly have a higher risk of exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) than those without antisocial tendencies. This may have been especially true early in the pandemic before vaccines against SARS-CoV-2 were available and before the emergence of the highly transmissible Omicron variant.
Introduction

Antisocial behavior (ASB)—including aggression, rule-breaking, delinquency, and violence—are harmful to society. ASB creates a long wake of monetary, social, and emotional disturbances for countries, communities, and individuals\(^1,2\). Especially troublesome are the possible effects during pandemics. For instance, ASB may abet pandemic spread. Those engaged in overt ASB seem to adhere less to coronavirus disease 2019 (COVID-19) containment measures\(^3-5\). Similarly, individuals scoring higher on less obvious indicators of antisociality (i.e., low acceptance of moral rules, higher levels of psychopathy, “pre-pandemic legal cynicism, low shame/guilt, low self-control, engagement in delinquent behaviors, and association with delinquent peers”) have shown evidence of disregarding public-health guidelines\(^3,4,6\). This warrants further investigation into the possible connections between ASB and exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19.

Complicating causal inference concerning the links between of ASB and pandemic-relevant outcomes is that about half of the variance in ASB and, to varying degrees, associated traits, is heritable\(^7-9\). This matters because the extent to which ASB and other traits share genetic architecture could influence the likelihood of genetic confounding in observational studies. Broadly addressing this problem is a nascent area of research that uses genome-wide association (GWA) studies of ASB and various health and behavioral traits to calculate genetic correlations (\(r_{gs}\))\(^10\). These studies have revealed \(r_{gs}\) between ASB and most psychiatric, psychological, reproductive, cognitive, and addictive traits\(^11,12\).

In addition, those prone to antisocial, violent, and criminal behaviors are disproportionately and profoundly unhealthy\(^13,14\). A strongly negative genetic correlation (\(r_g = -0.55\)) between ASB and self-reported health has been reported\(^11\). In contrast, a comprehensive study found no significant \(r_{gs}\) between ASB and 669 health, physiological, and well-being measures after accounting for multiple
testing\cite{15}. Thus, much remains to be discovered regarding shared etiology between ASB and various aspects of health, including COVID-19.

**Methods and materials**

We characterized the shared polygenic nature of ASB, COVID-19, and various health and behavioral traits using summary statistics from GWA studies and linkage disequilibrium score regression (LDSC; software available at [http://www.github.com/bulik/ldsc]http://www.github.com/bulik/ldsc\cite{16}). We calculated a matrix of $r_{gs}$. Of note is that correlation, even when genetic, is not necessarily causation. While our study can point to shared genetic architecture between traits, the reader should be cautious about assuming that the $r_{gs}$ are causal. **Table 1** contains details about the GWA studies we used and where interested researchers can access them. Nineteen traits were chosen for novelty (having not been previously reported as either null or significantly correlated with ASB). The novel traits include: average income (before taxes); healthspan (i.e., living free from congestive heart failure, myocardial infarction, chronic obstructive pulmonary disease [COPD], stroke, dementia, diabetes, cancer, and death; coded as a protective ratio); parental lifespan (hereafter “lifespan”; coded as a protective ratio); word interpolation (hereafter “verbal reasoning”); having been breastfed as baby; cheese intake; self-reported happiness; having had COVID-19 (data from two GWA studies); doing heavy manual labor; having a noisy workplace; Townsend Deprivation Index (an area- and census-based measure of deprivation, where a higher score indicates more deprivation); having gastrointestinal diseases; having COPD; having genitourinary diseases; playing computer games; having been a violent-crime victim; risk tolerance, and witnessing a sudden violent death. Four traits (education years; seen doctor for nerves, anxiety, tension, or depression; neuroticism; and Parkinson's disease) were chosen as replicates of previously reported findings.

**Results**
After false-discovery rate (FDR)-correction ($P < 0.05$), ASB was positively genetically correlated with COVID-19 (release 4): $r_g = 0.51$; $P = 1.54E-02$. The $r_g$ was also positive between ASB and COVID-19 (release 6) with marginal significance prior to FDR-correction but not after: $r_g = 0.35$; $P = 3.83E-02$ (FDR-corrected $P = 5.21E-02$). The remaining (FDR-significant) $r_g$ between ASB and health and behavioral traits that were positive are as follows:

1. Townsend Deprivation Index ($r_g = 0.70$)
2. Noisy workplace ($r_g = 0.63$)
3. Heavy manual labor ($r_g = 0.58$)
4. COPD ($r_g = 0.51$)
5. Risk tolerance ($r_g = 0.50$)
6. Gastrointestinal diseases ($r_g = 0.46$)
7. Seen a doctor for nerves, anxiety, tension, or depression ($r_g = 0.42$)
8. Seen a sudden violent death ($r_g = 0.42$)
9. Genitourinary diseases ($r_g = 0.38$)
10. Being a violent-crime victim ($r_g = 0.36$)
11. Neuroticism ($r_g = 0.29$)
12. Playing computer games ($r_g = 0.15$)

ASB was negatively genetically correlated with seven traits (after FDR-correction):

1. Average income ($r_g = -0.54$)
2. Education years ($r_g = -0.48$)
3. Healthspan ($r_g = -0.47$)
4. Verbal reasoning ($r_g = -0.44$)
5. Lifespan ($r_g = -0.33$)
6. Cheese intake ($r_g = -0.28$)
7. Breastfed as baby ($r_g = -0.24$)

The $r_{gs}$ for ASB and the health and behavioral traits are displayed in a forest plot in Figure 1 and presented in Table 2 along with confidence intervals and SNP-heritability ($h_g^2$) estimates. See the Supplement for the results for all the $r_{gs}$ in the matrix (Supplementary Table 1), including the $p$-values before and after FDR-correction (Supplementary Table 2).

**COVID-19**

Due to the positive $r_g$ between COVID-19 and ASB, we highlight the FDR-significant $r_{gs}$ between COVID-19 and non-ASB traits. COVID-19 was positively genetically correlated with the following:

1. COPD ($r_g = 0.40$) -- COVID-19 (release 6)
2. COPD ($r_g = 0.33$) -- COVID-19 (release 4)
3. Heavy manual labor ($r_g = 0.38$) -- COVID-19 (release 6)
4. Heavy manual labor ($r_g = 0.20$) -- COVID-19 (release 4)
5. Genitourinary diseases ($r_g = 0.32$) -- COVID-19 (release 6)
6. Noisy workplace ($r_g = 0.28$) -- COVID-19 (release 6)
7. Noisy workplace ($r_g = 0.26$) -- COVID-19 (release 4)

COVID-19 was negatively genetically correlated with the following:

1. Cheese intake ($r_g = -0.39$) -- COVID-19 (release 6)
2. Cheese intake ($r_g = -0.36$) -- COVID-19 (release 4)
3. Education years ($r_g = -0.46$) -- COVID-19 (release 6) 
4. Education years ($r_g = -0.32$) -- COVID-19 (release 4) 
5. Verbal reasoning ($r_g = -0.49$) -- COVID-19 (release 6) 
6. Verbal reasoning ($r_g = -0.28$) -- COVID-19 (release 4) 
7. Healthspan ($r_g = -0.41$) -- COVID-19 (release 6) 
8. Healthspan ($r_g = -0.25$) -- COVID-19 (release 4) 
9. Breastfed as baby ($r_g = -0.24$) -- COVID-19 (release 6) 
10. Lifespan ($r_g = -0.30$) -- COVID-19 (release 6) 
11. Average income ($r_g = -0.21$) -- COVID-19 (release 6) 

Notably, ASB and COVID-19 were both positively genetically correlated with having a noisy workplace, doing heavy manual labor, COPD, and genitourinary diseases. They were both inversely genetically correlated with average income, education years, healthspan, verbal reasoning, lifespan, cheese intake, and being breastfed as a baby. The $r_{gs}$ between COVID-19 and the non-ASB traits are presented in Figure 2 and Table 3 along with confidence intervals and $h_g^2$ estimates.

Discussion

In support of prior observational findings by O’Connell et al. (2021)$^5$, Carvalho and Machado (2020)$^3$, Miguel et al. (2021)$^4$, and Nivette et al. (2020)$^6$, the positive $r_g$ between ASB and COVID-19 suggests that those with antisocial tendencies are more likely to be exposed to SARS-CoV-2 than those who do not engage in ASB. Although ASB is generally associated with impulsive and risk-taking proclivities, the $r_g$ between COVID-19 and risk tolerance was null in our study, a result that argues against a propensity for risk-taking behavior underlying the link between ASB and exposure to SARS-CoV-2. The totality of our data instead suggests that a broad architecture of factors predispose some to
both ASB and COVID-19. Traits, for example, that are positively genetically correlated with both ASB
and COVID-19—having a noisy workplace, doing heavy manual labor, and having COPD—are also
strongly inversely genetically correlated with education years, verbal reasoning, and average income.

We observed positive $r_{gs}$ between ASB and the psychiatric and violence-related traits we
measured. But none of these traits were genetically correlated with COVID-19. That they were not
comports with a meta-analytic review of mood disorders and risk for COVID-19 in 91 million
individuals. Namely, Ceban et al. (2021) found no association between pre-existing mood disorders
and COVID-19. Thus, the link between ASB and COVID-19 is unlikely to be due to those engaging
in ASB having comorbid mood disorders.

We note that the strength of the $r_g$ for ASB and COVID-19 dropped from 0.51 (release 4) to
0.35 (release 6). Earlier GWA study releases by the COVID-19 Host Genetics Initiative capture data
from earlier timepoints in the pandemic—release 4 being earlier (October 20, 2020) than release 6
(June 15, 2021). This may be important since release 4 occurred before vaccines against SARS-CoV-2
were available, and by June 15, 2021, 47% of those eligible for vaccination had completed an initial
protocol for full vaccination in the U.S. Also, both releases 4 and 6 occurred prior to the appearance
of the more transmissible Omicron (B.1.1.529) variant, which most on the planet are expected to
encounter eventually. Thus, our results seem to reflect an increased risk of exposure to SARS-
CoV-2 early in the pandemic for those prone to ASB. If those with antisocial tendencies
disproportionately refuse vaccination against SARS-CoV-2, however, the impact of ASB over time
may have shifted from who gets exposed to SARS-CoV-2 to who gets severe disease.

Our study has limitations, which must also be considered. First is that the $h_g^2$ estimates for both
measures of COVID-19, while >0, were very small. This indicates that, based on the GWA results,
SNPs can only explain a very small proportion of the individual differences in risk for COVID-19.
Hence, although the $r_{gs}$ between ASB and COVID-19 were considerable, in absolute terms the genetic variance that is overlapping between the two traits is low. Second is that $r_{gs}$, while robust against most environmental confounders, can still suffer from genetic sources of confounding (i.e., even with $r_{gs}$, as we mentioned above, correlation is not necessarily causation). To illustrate, it seems unintuitive and unlikely that not being breastfed as a baby and eating less cheese cause ASB. One should, for somewhat obvious reasons, be similarly cautioned against the conclusion that being breastfed as a baby and eating more cheese protect against COVID-19, despite the apparent $r_{gs}$. Indeed, we chose these dietary traits to communicate the point that the shared genetic architecture that these have with education years, verbal reasoning, and average income seem the more plausibly causal phenomenon.

Third, supposing that some of the $r_{gs}$ represent causal linkages in some way, we nonetheless cannot determine the direction of causality with $r_{gs}$ alone. For much of the discussion above, we tacitly presumed plausible directions of effect (e.g., ASB causing exposure to SARS-CoV-2 and, thus, COVID-19 versus COVID-19 causing ASB). But with all the traits in our matrix, the prevailing direction of effect could be the opposite and/or some level of bi-directional causation may exist. And, as alluded to by “shared genetic architecture,” the correlated traits could be tagging a latent causal factor. These uncertainties are avenues for future research. Future studies could use either latent causal variable (LCV) models to infer causality between traits or perform bi-directional MR, an instrumental variables technique, for which both directions of effect are probed. Regarding MR, few genome-wide significant signals have been found for ASB, and using SNPs weakly associated with ASB as instrumental variables would violate the assumptions necessary to perform MR. But assuming SNPs strongly associated with ASB are eventually found, bi-directional MR can be used to decipher the prevailing directions of effect between ASB and traits with which it’s associated. A fourth limitation is that our findings are limited to those of European ancestry. The limitations
notwithstanding, $r_{gs}$ obtained from LDSC are not affected by sample overlap (i.e., participants being in both GWA studies for which the $r_{gs}$ were calculated)\textsuperscript{16}. This is a strength of study, which enabled us to capitalize on the power of large, population-based cohorts and publicly available GWA studies to probe timely questions. Finally, working to understand the etiology of ASB gets us closer to thinking about strategies to provide relief to a large part of the global population—both those engaged in ASB and those devastated by it.

Acknowledgements

We thank the consortia that made their GWA studies public.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Cohen MA. *The Costs of Crime and Justice*. 2nd edition. Routledge: New York, New York, 2020.
2. Koegl CJ, Farrington DP. Estimating the monetary cost of risk factors for crime in boys using the EARL-20B. *Psychol Serv* 2019; 18: 441–453.
3. Carvalho L de F, Machado GM. Differences in adherence to COVID-19 pandemic containment measures: psychopathy traits, empathy, and sex. *Trends Psychiatry Psychother* 2020; 42: 389–392.
4. Miguel FK, Machado GM, Pianowski G, Carvalho L de F. Compliance with containment measures to the COVID-19 pandemic over time: Do antisocial traits matter? *Pers Individ Dif* 2021; 168. doi:10.1016/j.paid.2020.110346.
5. O’Connell K, Berluti K, Rhoads SA, Marsh AA. Reduced social distancing early in the COVID-19 pandemic is associated with antisocial behaviors in an online United States sample. *PLoS ONE* 2021; 16. doi:10.1371/journal.pone.0244974.
6. Nivette A, Ribeaud D, Murray A, Steinhoff A, Bechtiger L, Hepp U *et al*. Non-compliance with COVID-19-related public health measures among young adults in Switzerland: insights from a longitudinal cohort study. *Soc Sci Med* 2021; 268. doi:10.1016/j.socscimed.2020.113370.
7. Burt SA. Are there meaningful etiological differences within antisocial behavior? Results of a meta-analysis. *Clin Psychol Rev* 2009; 29: 163–178.
8. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM *et al*. Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nat Genet* 2015; 47: 702–709.
9. Rhee SH, Waldman ID. Genetic and environmental influences on antisocial behavior: a meta-analysis of twin and adoption studies. *Psychol Bull* 2002; 128: 490–529.
10 Tielbeek JJ, Barnes JC, Popma A, Polderman TJC, Lee JJ, Perry JRB et al. Exploring the genetic correlations of antisocial behaviour and life history traits. BJPsych Open 2018; 4: 467–470.

11 Ip HF, van der Laan CM, Krapohl EML, Brikell I, Sánchez-Mora C, Nolte IM et al. Genetic association study of childhood aggression across raters, instruments, and age. Transl Psychiatry 2021; 11. doi:10.1038/s41398-021-01480-x.

12 Tielbeek JJ, Johansson A, Polderman TJC, Rautiainen MR, Jansen P, Taylor M et al. Genomewide association studies of a broad spectrum of antisocial behavior. JAMA Psychiatry 2017; 74: 1242–1250.

13 Massoglia M, Pridemore WA. Incarceration and health. Annu Rev Sociol 2015; 41: 291–310.

14 Vaughn MG, Salas-Wright CP, Delisi M, Maynard BR, Boutwell B. Prevalence and correlates of psychiatric disorders among former juvenile detainees in the United States. Compr Psychiatry 2015; 59: 107–116.

15 Tielbeek JJ, Boutwell BB. Exploring the genomic architectures of health, physical traits and antisocial behavioral outcomes: a brief report. Front Psychiatry 2020; 11. doi:10.3389/fpsyt.2020.00539.

16 Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR et al. An atlas of genetic correlations across human diseases and traits. Nat Genet 2015; 47: 1236–1241.

17 Ceban F, Nogo D, Carvalho IP, Lee Y, Nasri F, Xiong J et al. Association between mood disorders and risk of COVID-19 infection, hospitalization, and death: a systematic review and meta-analysis. JAMA Psychiatry 2021. doi:10.1001/jamapsychiatry.2021.1818.

18 Mathieu E, Ritchie H, Ortiz-Ospina E, Roser M, Hasell J, Appel C et al. A global database of COVID-19 vaccinations. Nat Hum Behav 2021; 5: 947–953.

19 Dejnirattisai W, Huo J, Zhou D, Zahradník J, Supasa P, Liu C et al. SARS-CoV-2 Omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses. Cell 2022; 185: 467–484.e15.

20 Aubrey A, Shapior A, Janse AM, Dorning C. Public health experts say most of us will get COVID-19. What does that mean? All Things Considered. NPR. 2022.https://www.npr.org/2022/01/12/1072548446/public-health-experts-say-most-of-us-will-get-covid-19-what-does-that-mean (accessed 19 Feb2022).

21 Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. Human Mol Genet 2018; 27: R195–R208.

22 O’Connor LJ, Price AL. Distinguishing genetic correlation from causation across 52 diseases and complex traits. Nat Genet 2018; 50: 1728–1734.

23 Pickrell JK, Berisa T, Liu JZ, Ségurel L, Tung JY, Hinds DA. Detection and interpretation of shared genetic influences on 42 human traits. Nat Genet 2016; 48: 709–717.

24 Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D et al. The MR-Base platform supports systematic causal inference across the human phenome. eLife 2018; 30: e34408.

25 Lyon M, Andrews S, Elsworth B, Gaunt T, Hemani G, Marcora E. The variant call format provides efficient and robust storage of GWAS summary statistics. bioRxiv 2020. doi:10.1101/2020.05.29.115824.

26 Elsworth B, Lyon M, Alexander T, Liu Y, Matthews P, Hallett J et al. The MRC IEU OpenGWAS data infrastructure. bioRxiv 2020. doi:10.1101/2020.08.10.244293.

27 Okbay A, Beauchamp JP, Fontana MA, Lee JJ, Pers TH, Rietveld CA et al. Genome-wide association study identifies 74 loci associated with educational attainment. Nature 2016; 533: 539–542.
Karlsson Linér R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA et al. Genomewide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. Nat Genet 2019; 51: 245–257.

Zenin A, Tsepilov Y, Sharapov S, Getmantsev E, Menshikov LI, Fedichev PO et al. Identification of 12 genetic loci associated with human healthspan. Commun Biol 2019; 2. doi:10.1038/s42003-019-0290-0.

Timmers PR, Mounier N, Lall K, Fischer K, Ning Z, Feng X et al. Genomics of 1 million parent lifespans implicates novel pathways and common diseases and distinguishes survival chances. eLife 2019; 15. doi:10.7554/eLife.39856.001.

Nalls MA, Blauwendraat C, Vallerga CL, Heilbron K, Bandres-Ciga S, Chang D et al. Identification of novel risk loci, causal insights, and heritable risk for Parkinson’s disease: a meta-analysis of genome-wide association studies. Lancet Neurol 2019; 18: 1091–1102.

COVID-19 Host Genetics Initiative. Mapping the human genetic architecture of COVID-19. Nature 2021. doi:10.1038/s41586-021-03767-x.

Tielbeek JJ, Uffelmann E, Williams BS, Colodro-Conde L, Gagnon É, Mallard TT et al. Uncovering the genetic architecture of broad antisocial behavior through a genome-wide association study meta-analysis. bioRxiv 2021. doi:10.1101/2021.10.19.462578.
Table 1. GWA study data sources.

| Trait (abbreviation)                               | Data source: Consortium and Availability                                                                                                                                                                                                 | Effective Sample Size |
|----------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Average total household income before tax          | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-7408; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                 | 397,751               |
| Education years                                    | Okbay et al. (2016)\(^2\); Social Science Genetic Association Consortium (SSGAC); https://www.thessgac.org/\(^2\)                                                                                                                                 | 293,723               |
| Healthspan                                         | Zenin et al. (2019)\(^2\); (UKBB; n=300,447 European); https://www.gwasarchive.org/                                                                                                                                                     | 300,447               |
| Lifespan                                           | Timmers et al.\(^3\) (2019); UKBB/LifeGen study; https://datashare.ed.ac.uk/handle/10283/3209                                                                                                                                             | 1,012,240             |
| Word interpolation (“verbal reasoning”)            | UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-d-4957; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                 | 98,753 cases and 18,062 controls |
| Breastfed as baby                                  | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-13423; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                          | 251,150 cases and 100,944 controls |
| Cheese intake                                      | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-1489; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                            | 451,486               |
| Self-rated happiness (“happiness”)                 | UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-a-367; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                     | 110,935               |
| Parkinson's disease                                | Nalls et al. (2019)\(^3\); International Parkinson's Disease Genomics Consortium; IEU Open GWAS Project identifier: ieu-b-7; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                              | 33,674 cases and 449,046 controls |
| COVID-19                                            | COVID-19 Host Genetics Initiative, release 4\(^2\); IEU Open GWAS Project identifier: ebi-a-GCST010780; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                       | 14,134 COVID-19 cases and 1,284,876 controls (release 4) SNPs=12,500,447 |
| COVID-19                                            | COVID-19 Host Genetics Initiative, release 6\(^2\) https://www.covid19hg.org/results/r6/                                                                                                                                                 | 112,612 COVID-19 cases and 2,474,079 controls (release 6) SNPs= 8,141,092 |
| Job involves heavy manual or physical work (“heavy manual labor”) | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-2002; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                       | 263,615               |
| Noisy workplace                                     | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-2091; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                       | 151,624               |
| ASB                                                | Broad Antisocial Behavior Consortium (BroadABC); http://broadabc.ctglab.nl/ (data available upon request)\(^1\)\(^,\)\(^3\)                                                                                                           | 56,575                |
| Townsend Deprivation Index                         | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-10011; https://gwas.mrcieu.ac.uk/datasets/24-26                                                                                                                                       | 462,464               |
| Gastrointestinal diseases                          | FINNGen Biobank analysis; 39,639 cases and 56,860 controls (European); binary; IEU Open                                                                                                                                             | 39,639 cases and 56,860 controls |
| GWAS Project identifier: finn-a-K11_GIDISEASES; https://www.finngen.fi/fi/ | Chronic obstructive pulmonary disease (COPD) differential diagnosis | UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-d-COPD_EXCL; https://gwas.mrcieu.ac.uk/datasets | 26,710 cases and 334,484 controls |
| --- | --- | --- | --- |
| GWAS Project identifier: ukb-d-XIV_GENITOURINARY; https://gwas.mrcieu.ac.uk/datasets | Genitourinary diseases | UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-d-XIV_GENITOURINARY; https://gwas.mrcieu.ac.uk/datasets | 71,620 cases and 289,574 controls |
| GWAS Project identifier: ukb-b-4630; https://gwas.mrcieu.ac.uk/datasets | Neuroticism score (“neuroticism”) | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-4630; https://gwas.mrcieu.ac.uk/datasets | 374,323 |
| GWAS Project identifier: ukb-b-6991; https://gwas.mrcieu.ac.uk/datasets | Seen doctor for nerves, anxiety, tension, or depression | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-6991; https://gwas.mrcieu.ac.uk/datasets | 158,565 cases and 300,995 controls |
| GWAS Project identifier: ukb-b-4779; https://gwas.mrcieu.ac.uk/datasets | Plays computer games | MRC-IEU; IEU Open GWAS Project identifier: ukb-b-4779; https://gwas.mrcieu.ac.uk/datasets | 462,433 |
| GWAS Project identifier: ukb-d-20529; https://gwas.mrcieu.ac.uk/datasets | Victim of physically violent crime (“violent-crime victim”) | UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-d-20529; https://gwas.mrcieu.ac.uk/datasets | 21,926 cases and 95,920 controls |
| Karlsson Linnér et al. (2019)[30]; Social Science Genetic Association Consortium (SSGAC); https://www.thessgac.org/ | Risk tolerance (self-rated: “Would you describe yourself as someone who takes risks?”) | | 466,571 |
| GWAS Project identifier: ukb-d-20530; https://gwas.mrcieu.ac.uk/datasets | Witnessed sudden violent death (“saw sudden violent death”) | UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-d-20530; https://gwas.mrcieu.ac.uk/datasets | 15,959 cases and 101,903 controls |

UKBB = UK Biobank; IEU = Medical Research Counsel Integrative Epidemiology Unit at the University of Bristol; GWAS = genome-wide association study. Most of the GWA studies were performed solely in those of European ancestry. The two COVID-19 GWA studies came from meta-analyses that predominately consisted of those of European ancestry, but the COVID-19 (release 6) included some participants of other ancestral backgrounds. However, the COVID-19 Host Genetics Initiative cohort that generated the COVID-19 data performed sensitivity analyses generating SNP-heritability ($h^2_g$) estimates for COVID-19 using only the data for those of European ancestry for release 6 and compared these to the $h^2_g$ estimates for the meta-analytic measures we used: the $h^2_g$ estimates were nearly the same (see the Supplementary table 6 that accompanies the COVID-19 Host Genetics Initiative paper[32]). Were the $h^2_g$ estimates substantially different, use of the meta-analytic data for LDSC would have been inappropriate. Thus, though we did not have access to the European-only
ancestry data for COVID-19 (release 6), the $h^2_\gamma$ estimates for the meta-analytic data do not appear to be confounded by mixed ancestries.
Table 2. Genetic correlations \( (r_g) \) between ASB and health and behavioral traits.

| Trait 1                  | Trait 2              | \( r_g \) | Lower 95\% CI for \( r_g \) | Upper 95\% CI for \( r_g \) | FDR \( P \)-value | \( h_g^2 \) for trait 2 |
|-------------------------|----------------------|-----------|------------------------------|-------------------------------|--------------------|--------------------------|
| ASB                     | Average income       | -0.54     | -0.65                        | -0.43                         | 9.88E-22           | 0.07                     |
| ASB                     | Education years      | -0.48     | -0.59                        | -0.38                         | 9.76E-20           | 0.12                     |
| ASB                     | Healthspan           | -0.47     | -0.62                        | -0.31                         | 5.97E-09           | 0.03                     |
| ASB                     | Verbal reasoning     | -0.44     | -0.58                        | -0.30                         | 5.62E-09           | 0.08                     |
| ASB                     | Lifespan             | -0.33     | -0.46                        | -0.21                         | 4.20E-07           | 0.02                     |
| ASB                     | Cheese intake        | -0.28     | -0.38                        | -0.18                         | 6.97E-08           | 0.07                     |
| ASB                     | Breastfed as baby    | -0.24     | -0.38                        | -0.11                         | 9.60E-04           | 0.03                     |
| ASB                     | Happiness            | -0.10     | -0.25                        | 0.05                          | 2.22E-01           | 0.06                     |
| ASB                     | Parkinson's disease  | -0.04     | -0.26                        | 0.18                          | 7.77E-01           | 0.02                     |
| ASB                     | Plays computer games | 0.15      | 0.06                         | 0.25                          | 3.60E-03           | 0.07                     |
| ASB                     | Neuroticism          | 0.29      | 0.20                         | 0.38                          | 3.05E-10           | 0.11                     |
| ASB                     | COVID-19 (release 6) | 0.35      | 0.02                         | 0.68                          | 5.21E-02           | 0.001                    |
| ASB                     | Violent-crime victim | 0.36      | 0.16                         | 0.56                          | 5.82E-04           | 0.03                     |
| ASB                     | Genitourinary diseases | 0.38   | 0.22                         | 0.55                          | 1.45E-05           | 0.02                     |
| ASB                     | Saw sudden violent death | 0.42 | 0.20                         | 0.65                          | 3.95E-04           | 0.02                     |
| ASB                     | Seen doctor for nerves, anxiety, tension, or depression | 0.42 | 0.31 | 0.54 | 2.36E-13 | 0.06 |
| ASB                     | Gastrointestinal diseases | 0.46 | 0.23 | 0.70 | 1.89E-04 | 0.04 |
| ASB                     | Risk tolerance       | 0.50      | 0.39                         | 0.60                          | 6.34E-20           | 0.02                     |
| ASB                     | COPD                 | 0.51      | 0.33                         | 0.68                          | 6.45E-08           | 0.01                     |
| ASB                     | COVID-19 (release 4) | 0.51      | 0.12                         | 0.90                          | 1.54E-02           | 0.001                    |
| ASB                     | Heavy manual labor   | 0.58      | 0.45                         | 0.70                          | 8.31E-19           | 0.08                     |
| ASB                     | Noisy workplace      | 0.63      | 0.48                         | 0.77                          | 3.99E-16           | 0.06                     |
| ASB                     | Townsend Deprivation Index | 0.70 | 0.56 | 0.84 | 2.25E-22 | 0.03 |

ASB = antisocial behavior; \( r_g \) = genetic correlation; FDR = false-discovery rate (corrected) \( P \)-value; \( h_g^2 \) = SNP-heritability.
### Table 3. Genetic correlations ($r_g$) between COVID-19 and health and behavioral traits.

| Trait 1                  | Trait 2                                      | $r_g$ | Lower 95% CI for $r_g$ | Upper 95% CI for $r_g$ | FDR $P$-value | $h_g^2$ for trait 2 |
|--------------------------|----------------------------------------------|-------|-------------------------|------------------------|----------------|---------------------|
| COVID-19 (release 6)     | Chronic obstructive pulmonary disease        | 0.40  | 0.11                    | 0.70                   | 1.17E-02       | 0.02                |
| COVID-19 (release 6)     | Heavy manual labor                           | 0.38  | 0.19                    | 0.56                   | 1.25E-04       | 0.08                |
| COVID-19 (release 4)     | Chronic obstructive pulmonary disease        | 0.33  | 0.04                    | 0.61                   | 3.44E-02       | 0.01                |
| COVID-19 (release 6)     | Genitourinary diseases                       | 0.32  | 0.04                    | 0.60                   | 3.69E-02       | 0.02                |
| COVID-19 (release 6)     | Noisy workplace                              | 0.28  | 0.07                    | 0.50                   | 1.45E-02       | 0.06                |
| COVID-19 (release 4)     | Noisy workplace                              | 0.26  | 0.03                    | 0.49                   | 3.69E-02       | 0.06                |
| COVID-19 (release 6)     | Saw sudden violent death                     | 0.25  | -0.08                   | 0.58                   | 1.70E-01       | 0.03                |
| COVID-19 (release 6)     | Violent-crime victim                         | 0.23  | -0.09                   | 0.55                   | 1.97E-01       | 0.03                |
| COVID-19 (release 4)     | Genitourinary diseases                       | 0.21  | -0.03                   | 0.45                   | 1.17E-01       | 0.02                |
| COVID-19 (release 4)     | Heavy manual labor                           | 0.20  | 0.03                    | 0.37                   | 2.65E-02       | 0.08                |
| COVID-19 (release 6)     | Gastrointestinal diseases                    | 0.20  | -0.10                   | 0.49                   | 2.36E-01       | 0.05                |
| COVID-19 (release 6)     | Townsend Deprivation Index                   | 0.18  | -0.05                   | 0.41                   | 1.66E-01       | 0.03                |
| COVID-19 (release 6)     | Risk tolerance                               | 0.14  | -0.03                   | 0.31                   | 1.31E-01       | 0.02                |
| COVID-19 (release 4)     | Townsend Deprivation Index                   | 0.08  | -0.11                   | 0.27                   | 4.81E-01       | 0.03                |
| COVID-19 (release 4)     | Risk tolerance                               | 0.07  | -0.10                   | 0.24                   | 4.97E-01       | 0.02                |
| COVID-19 (release 4)     | Happiness                                    | 0.06  | -0.19                   | 0.30                   | 7.07E-01       | 0.06                |
| COVID-19 (release 6)     | Seen doctor for nerves, anxiety, tension, or depression | 0.05  | -0.09                   | 0.18                   | 5.40E-01       | 0.06                |
| COVID-19 (release 4)     | Seen doctor for nerves, anxiety, tension, or depression | 0.03  | -0.11                   | 0.17                   | 7.22E-01       | 0.06                |
| COVID-19 (release 6)     | Happiness                                    | 0.03  | -0.21                   | 0.27                   | 8.38E-01       | 0.06                |
| COVID-19 (release 4)     | Parkinson's disease                          | 0.01  | -0.26                   | 0.27                   | 9.39E-01       | 0.02                |
| COVID-19 (release 4)     | Plays computer games                         | -0.03 | -0.17                   | 0.11                   | 7.19E-01       | 0.07                |
| COVID-19 (release 6)     | Plays computer games                         | -0.04 | -0.17                   | 0.09                   | 6.23E-01       | 0.08                |
| COVID-19 (release 6)     | Neuroticism                                  | -0.04 | -0.16                   | 0.08                   | 5.25E-01       | 0.11                |
| COVID-19 (release 6)     | Parkinson's disease                          | -0.06 | -0.28                   | 0.16                   | 6.61E-01       | 0.02                |
| COVID-19 (release 4)     | Gastrointestinal diseases                    | -0.08 | -0.39                   | 0.24                   | 7.06E-01       | 0.04                |
| COVID-19 (release 4)     | Neuroticism                                  | -0.09 | -0.26                   | 0.08                   | 3.68E-01       | 0.11                |
| COVID-19 (release 4)     | Average income                               | -0.16 | -0.32                   | 0.00                   | 6.02E-02       | 0.07                |
| COVID-19 (release 4)     | Lifespan                                     | -0.17 | -0.37                   | 0.04                   | 1.47E-01       | 0.02                |
| COVID-19 (release 4)     | Breastfed as baby                            | -0.17 | -0.41                   | 0.06                   | 1.93E-01       | 0.03                |
| COVID-19 (release 6)     | Average income                               | -0.21 | -0.37                   | -0.04                  | 2.06E-02       | 0.07                |
| COVID-19 (release 4)     | Violent-crime victim                         | -0.24 | -0.58                   | 0.11                   | 2.24E-01       | 0.03                |
| COVID-19 (release 6)     | Breastfed as baby                            | -0.24 | -0.46                   | -0.03                  | 3.69E-02       | 0.02                |
| COVID-19 (release 4)     | Heathspan                                    | -0.25 | -0.45                   | -0.04                  | 2.53E-02       | 0.03                |
| COVID-19 (release 4)     | Verbal reasoning                             | -0.28 | -0.52                   | -0.03                  | 3.79E-02       | 0.08                |
| COVID-19 (release 6)     | Lifespan                                     | -0.30 | -0.48                   | -0.11                  | 2.73E-03       | 0.02                |
| COVID-19 (release 4)     | Saw sudden violent death                     | -0.30 | -0.68                   | 0.07                   | 1.50E-01       | 0.03                |
| COVID-19 (release 4)     | Education years                              | -0.32 | -0.48                   | -0.16                  | 1.39E-04       | 0.13                |
| COVID-19 (release 4)     | Cheese intake                                | -0.36 | -0.56                   | -0.16                  | 9.65E-04       | 0.07                |
| COVID-19 (release 6)     | Cheese intake                                | -0.39 | -0.59                   | -0.20                  | 1.88E-04       | 0.07                |
| COVID-19 (release 6)     | Heathspan                                    | -0.41 | -0.62                   | -0.20                  | 2.23E-04       | 0.03                |
| COVID-19 (release 6)     | Education years                              | -0.46 | -0.66                   | -0.26                  | 1.09E-05       | 0.13                |
| COVID-19 (release 6)     | Verbal reasoning                             | -0.49 | -0.76                   | -0.22                  | 6.28E-04       | 0.09                |

$r_g$ = genetic correlation; FDR = false-discovery rate (corrected) $P$-value; $h_g^2$ = SNP-heritability.
Genetic correlations (95% confidence intervals) for ASB and health and behavioral traits. Closed circles indicate false-discovery rate (corrected) $P < 0.05$. 

- Townsend Deprivation Index
- Noisy workplace
- Heavy manual labor
- COVID-19 (round 4)
- Chronic obstructive pulmonary disease
- Risk tolerance
- Gastrointestinal diseases
- Seen doctor for nerves, anxiety, tension, or depression
- Saw sudden violent death
- Genitourinary diseases
- Violent-crime victim
- COVID-19 (round 6)
- Neuroticism
- Plays computer games
- Parkinson's disease
- Happiness
- Breastfed as baby
- Cheese intake
- Lifespan
- Verbal reasoning
- Healthspan
- Education years
- Average income

Category
- Replication
- Novel
Genetic correlations (95% confidence intervals) for COVID-19 and health and behavioral traits. Closed circles indicate false-discovery rate (corrected) $P < 0.05$. 

- Antisocial behavior
- Chronic obstructive pulmonary disease
- Heavy manual labor
- Genitourinary diseases
- Noisy workplace
- Saw sudden violent death
- Violent-crime victim
- Gastrointestinal diseases
- Townsend Deprivation Index
- Risk tolerance
- Happiness
- Seen doctor for nerves, anxiety, tension, or depression
- Parkinson's disease
- Plays computer games
- Neuroticism
- Average income
- Lifespan
- Breastfed as baby
- Healthspan
- Verbal reasoning
- Education years
- Cheese intake