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Shared genomic architectures of COVID-19 and antisocial behavior

Charleen D. Adams[1]✉, Jorim J. Tielbeek[2], Brian B. Boutwell[3,4] and Broad Antisocial Behavior Consortium

Little is known about the genetics of norm violation and aggression 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 antisocial behavior (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^2_g) estimates for two measures of COVID-19 were very small, restricting the overlap of genetic variance in absolute terms between ASB and COVID-19. 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.

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INTRODUCTION

Antisocial behavior (ASB)—including rule-breaking and violence—is harmful to society. ASB creates a long wake of monetary 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 (e.g., low acceptance of moral rules and higher levels of psychopathy) 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 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 health and behavioral traits to calculate genetic correlations (r_{gs}) [10]. These studies have revealed r_{gs} between ASB and most psychiatric, reproductive, cognitive, and addictive traits [11, 12]. In addition, those prone to antisocial 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 [15]. Thus, much remains to be discovered regarding shared etiology between ASB and aspects of health, including COVID-19.

METHODS AND MATERIALS

We characterized the shared polygenic nature of ASB, COVID-19, and selected 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) [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

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Table 1. GWA study data sources.

Trait (abbreviation)	Data source: Consortium and Availability	Effective Sample Size
Average total household income before tax ("average income")	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) [27]; Social Science Genetic Association Consortium (SSGAC); https://www.thessgac.org/ [28]	293,723
Healthspan	Zenin et al. (2019) [29]; (UKBB; $n = 300{,}447$ European); https://www.gwasarchive.org/	300,447
Lifespan	Timmers et al. [30] (2019); UKBB/LifeGen study; https://datashare.ed.ac.uk/handle/10283/3209	Up to 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) [31]. 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 [32, 33]; 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)
COVID-19	COVID-19 Host Genetics Initiative, release 6 [32, 33] https://www.covid19hg.org/results/r6/	112,612 COVID-19 cases and 2,474,079 controls (release 6)
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) [12, 34]	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 GWAS Project identifier: finn-a-K11_GIDISEASES; https://www.finngen.fi/fi/ [24–26]	39,639 cases and 56,860 controls
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/ [24–26]	26,710 cases and 334,484 controls
Genitourinary diseases	UKBB/Neale lab; IEU Open GWAS Project identifier: ukb-d-XIV_GENITOURINARY; https://gwas.mrcieu.ac.uk/datasets/ [24–26]	71,620 cases and 289,574 controls
Neuroticism score ("neuroticism")	MRC-IEU; IEU Open GWAS Project identifier: ukb-b-4630; https://gwas.mrcieu.ac.uk/datasets/ [24–26]	374,323
Seen doctor for nerves, anxiety, tension, or depression	MRC-IEU; IEU Open GWAS Project identifier: ukb-b-6991; https://gwas.mrcieu.ac.uk/datasets/ [24–26]	158,565 cases and 300,995 controls
Plays computer games	MRC-IEU; IEU Open GWAS Project identifier: ukb-b-4779; https://gwas.mrcieu.ac.uk/datasets/ [24–26]	462,433
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/ [24–26]	21,926 cases and 95,920 controls
Risk tolerance (self-rated: "Would you describe yourself as someone who takes risks?")	Karlsson Linnér et al. (2019) [28]; Social Science Genetic Association Consortium (SSGAC); https://www.thessgac.org/	466,571
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/ [24–26]	15,959 cases and 101,903 controls

UKBB = UK Biobank; MRC-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_g estimates for the meta-analytic data do not appear to be confounded by mixed ancestries.

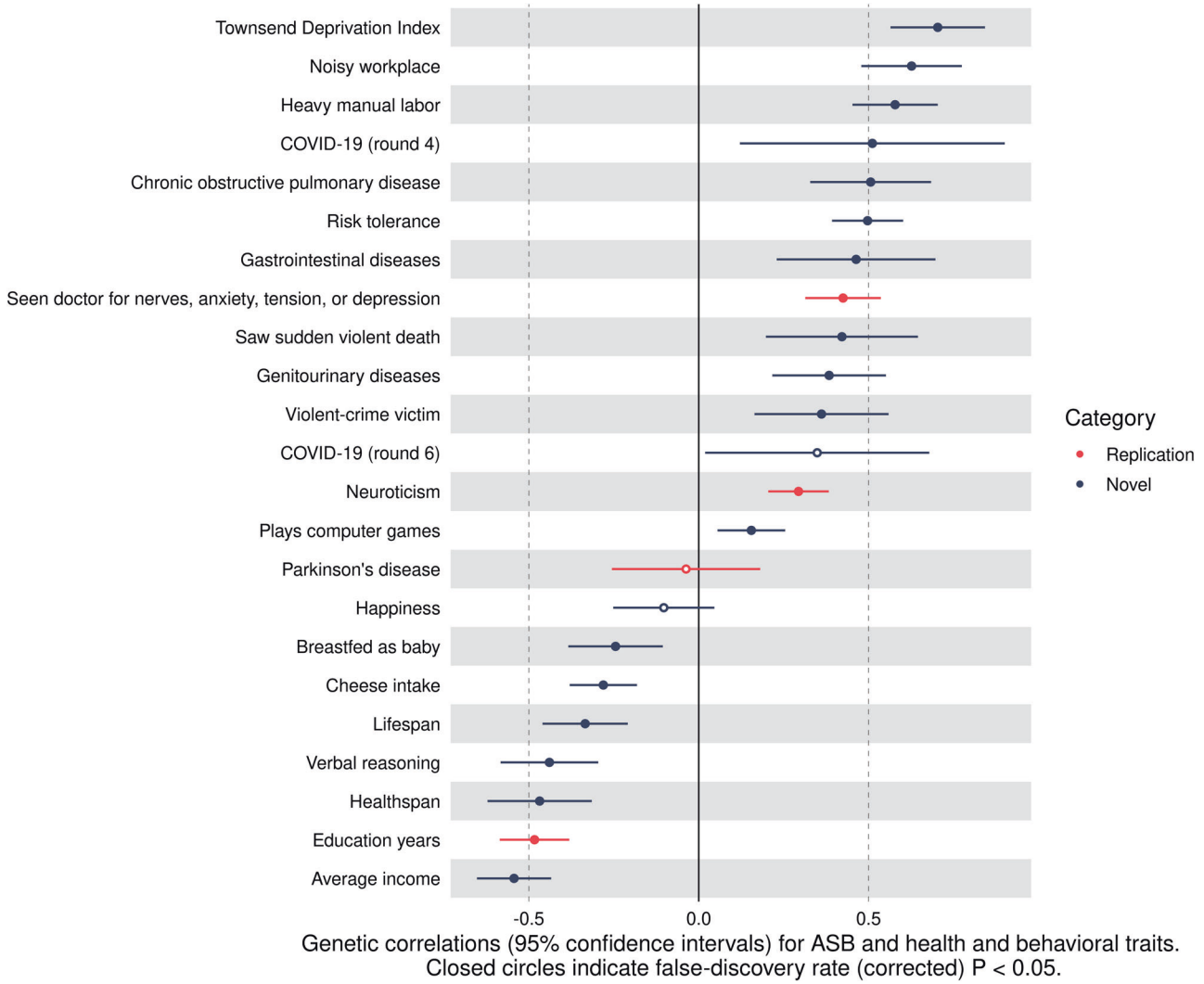

Fig. 1 Genetic correlations and 95% confidence intervals for ASB and health and behavioral traits. Closed circles indicate false-discovery rate (corrected) *P*-values (<0.05).

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 a 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

ASB

After false-discovery rate (FDR)-correction ($P < 0.05$), ASB was positively genetically correlated with COVID-19 (release 4): $r_g =$ 0.51; $P = 1.54E\text{-}02$. The r_g was also positive between ASB and COVID-19 (release 6) with marginal significance *prior* to FDR-correction but not after: $r_g = 0.35$; $P = 3.83E\text{-}02$ (FDR-corrected $P = 5.21E\text{-}02$). The remaining (FDR-significant) r_{gs} between ASB and health and behavioral traits that were positively genetically correlated 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 ($r_g = -0.24$)

Table 2. Genetic correlations (r_{gs}) for 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.

The r_{gs} for ASB and the health and behavioral traits are displayed in a forest plot in Fig. 1 and presented in Table 2 along with confidence intervals and SNP-heritability (h_g^2) estimates. See the Supplement for all traits 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 Fig. 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

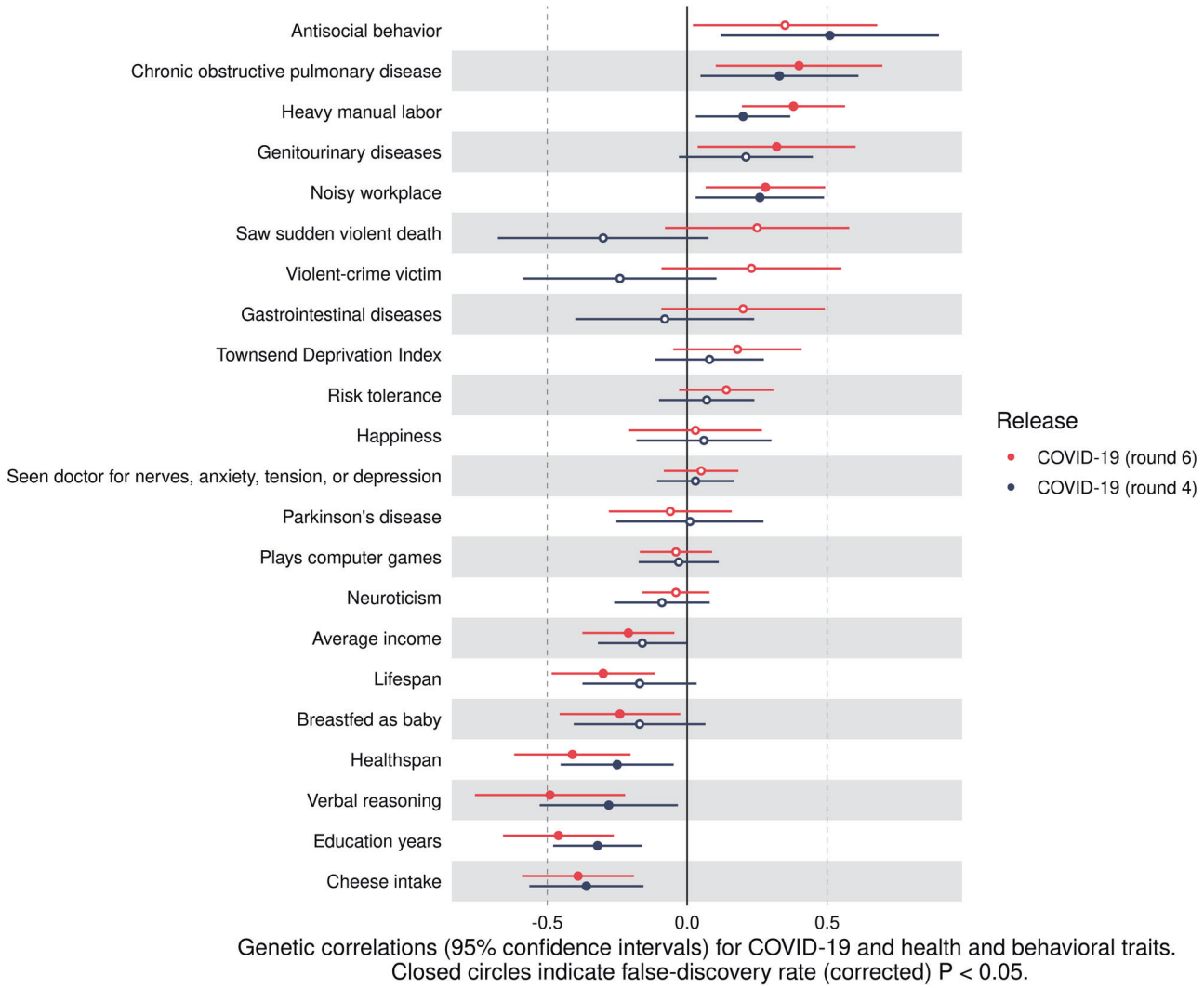

Fig. 2 Genetic correlations and 95% confidence intervals for COVID-19 and health and behavioral traits. Closed circles indicate false-discovery rate (corrected) *P*-values (<0.05).

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 [17]. Namely, Ceban et al. (2021) found no association between pre-existing mood disorders and COVID-19 [17]. 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 [18]. 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 [19, 20]. 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 SNPs only explain a tiny 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, likewise, small. 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 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 significant r_{gs}. Indeed, we chose these dietary traits to communicate the point that the shared genetic architectures that these have with education years, verbal reasoning, and average income seem the more plausibly causal phenomena. Third, supposing that some of the r_{gs} represent causal linkages in some way, we nonetheless cannot determine the

Table 3. Genetic correlations (r_{gs}) 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	9.59E-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)	Healthspan	−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

Table 3. continued

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)	Cheese intake	−0.39	−0.59	−0.20	1.88E-04	0.07
COVID-19 (release 6)	Healthspan	−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.

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 [16, 21–23]. 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) [22] 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) [16]. This is a strength of this study, which enabled us to capitalize on the power of large, population-based cohorts and publicly available GWA studies. Another strength is that 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.

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AUTHOR CONTRIBUTIONS

CDA conceived of the study, performed the analyses, created the figures and tables, and drafted the original manuscript. JJT, BBB, and CDA edited and revised the manuscript. All authors approved the final manuscript. BBB coordinated and supervised the project.

COMPETING INTERESTS

The authors declare no competing interests.

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