

This is an electronic reprint of the original article. This reprint may differ from the original in pagination and typographic detail.

Uncovering the genetic architecture of broad antisocial behavior through a genome-wide association study meta-analysis

Tielbeek, Jorim; Uffelmann, Emil; Williams, Benjamin; Colodro-Conde, Lucia; Gagnon, Eloi; Mallard, Travis; Levitt, Brandt; Jansen, Philip; Johansson, Ada; Sallis, Hannah; Pistis, Giorgio; Saunders, Gretschen; Allegrini, Andrea; Rimfeld, Kaili; Konte, Bettina; Klein, Marieke; Hartmann, Annette; Salvatore, Jessica; Nolte, Ilja; Demontis, Ditte; Malmberg, Anni; Burt, Alexandra; Savage, Jeanne; Sugden, Karen; Poulton, Richie; Mullan Harris, Kathleen; Vrieze, Scott; McGue, Matt; Iacono, William; Roth Mota, Nina; Mill, Jonathan; Viana, Joana; Mitchell, Brittany; Morosoli, Jose; Andlauer, Till; Ouellet-Morin, Isabelle; Tremblay, Richard; Côté, Sylvana; Gouin, Jean-Philippe; Brendgen, Mara; Dionne, Ginette; Vitaro, Frank; Lupton, Michelle; Martin, Nicholas; COGA Consortium; Spit for Science Working Group; Castela, Enrique; Rääkkönen, Katri; Eriksson, Johan; Lahti, Jari; Hartman, Catharina; Oldehinkel, Albertine; Snieder, Harold; Liu, Hexuan; Preisig, Martin; Whipp, Alyce; Vuoksimaa, Eero; Lu, Yi; Jern, Patrik; Rujescu, Dan; Giegling, Ina; Palviainen, Teemu; Kaprio, Jaakko; Paige Harden, Kathryn; Munafò, Marcus; Morneau-Vaillancourt, Geneviève; Plomin, Robert; Viding, Essi; Boutwell, Brian; Aliev, Fazil; Dick, Danielle; Popma, Arne; Faraone, Stephen; Børglum, Anders; Medland, Sarah; Franke, Barbara; Boivin, Michel; Pingault, Jean-Baptiste; Glennon, Jeffrey; Barnes, J. C.; Fisher, Simon; Moffitt, Terrie; Caspi, Avshalom; Polderman, Tinca; Posthuma, Danielle

Published in:
Molecular Psychiatry

Published: 01/01/2022

Document Version
Accepted author manuscript

Document License
Publisher rights policy

[Link to publication](#)

Please cite the original version:

Tielbeek, J., Uffelmann, E., Williams, B., Colodro-Conde, L., Gagnon, E., Mallard, T., Levitt, B., Jansen, P., Johansson, A., Sallis, H., Pistis, G., Saunders, G., Allegrini, A., Rimfeld, K., Konte, B., Klein, M., Hartmann, A., Salvatore, J., Nolte, I., ... Posthuma, D. (2022). Uncovering the genetic architecture of broad antisocial behavior through a genome-wide association study meta-analysis. *Molecular Psychiatry*, 27, 4453-4463. <https://www.nature.com/articles/s41380-022-01793-3>

1 **Uncovering the Genetic Architecture of Broad Antisocial Behavior**
2 **through a Genome-Wide Association Study Meta-analysis.**

3 **Authors:** Jorim J. Tielbeek, Emil Uffelmann, Benjamin S. Williams, Lucía Colodro-Conde,
4 Éloi Gagnon, Travis T. Mallard, Brandt Levitt, Philip R. Jansen, Ada Johansson, Hannah
5 Sallis, Giorgio Pistis, Gretchen R.B. Saunders, Andrea G Allegrini, Kaili Rimfeld, Bettina
6 Konte, Marieke Klein, Annette M. Hartmann, Jessica E Salvatore, Ilja M. Nolte, Ditte
7 Demontis, Anni Malmberg, S. Alexandra Burt, Jeanne Savage, Karen Sugden, Richie
8 Poulton, Kathleen Mullan Harris, Scott Vrieze, Matt McGue, William G. Iacono, Nina Roth
9 Mota, Jonathan Mill, Joana F. Viana, Brittany L Mitchell, Jose J Morosoli, Till Andlauer,
10 Isabelle Ouellet-Morin, Richard E. Tremblay, Sylvana Côté, Jean-Philippe Gouin, Mara
11 Brendgen, Ginette Dionne, Frank Vitaro, Michelle K Lupton, Nicholas G Martin, COGA
12 Consortium, Spit for Science Working Group, Enrique Castela, Katri Räikkönen, Johan
13 Eriksson, Jari Lahti, Catharina A Hartman, Albertine J. Oldehinkel, Harold Snieder, Hexuan
14 Liu, Martin Preisig, Alyce Whipp, Eero Vuoksimaa, Yi Lu, Patrick Jern, Dan Rujescu, Ina
15 Giegling, Teemu Palviainen, Jaakko Kaprio, Kathryn Paige Harden, Marcus R. Munafò,
16 Geneviève Morneau-Vaillancourt, Robert Plomin, Essi Viding, Brian Boutwell, Fazil Aliev,
17 Danielle Dick, Arne Popma, Stephen V Faraone, Anders Børghlum, Sarah E Medland, Barbara
18 Franke, Michel Boivin, Jean-Baptiste Pingault, Jeffrey C Glennon, James C. Barnes, Simon
19 E. Fisher, Terrie E. Moffitt, Avshalom Caspi, Tinca JC Polderman, Danielle Posthuma,
20 *Broad Antisocial Behavior Consortium collaborators*

21

22 Correspondence to: Jorim J. Tielbeek, Department of Complex Trait Genetics, Vrije
23 Universiteit Amsterdam, De Boelelaan 1085, 1081 HV, Amsterdam, The Netherlands.

24 E-mail: j.j.tielbeek@vu.nl

25

26

27

28

29

30 **Abstract**

31 Despite the substantial heritability of antisocial behavior (ASB), specific genetic variants robustly
32 associated with the trait have not been identified. The present study by the Broad Antisocial Behavior
33 Consortium (BroadABC) meta-analyzed data from 28 discovery samples ($N = 85,359$) and five
34 independent replication samples ($N = 8,058$) with genotypic data and broad measures of ASB. We
35 identified the first significant genetic associations with broad ASB, involving common intronic
36 variants in the forkhead box protein P2 (*FOXP2*) gene (lead SNP rs12536335, $P = 6.32 \times 10^{-10}$).
37 Furthermore, we observed intronic variation in *Foxp2* and one of its targets (*Cntnap2*) distinguishing
38 a mouse model of pathological aggression (BALB/cJ strain) from controls (BALB/cByJ strain). The
39 SNP-based heritability of ASB was 8.4% (s.e.= 1.2%). Polygenic-risk-score (PRS) analyses in
40 independent samples revealed that the genetic risk for ASB was associated with several antisocial
41 outcomes across the lifespan, including diagnosis of conduct disorder, official criminal convictions,
42 and trajectories of antisocial development. We found substantial genetic correlations of ASB with
43 mental health (depression $r_g = 0.63$, insomnia $r_g = 0.47$), physical health (overweight $r_g = 0.19$,
44 waist-to-hip ratio $r_g = 0.32$), smoking ($r_g = 0.54$), cognitive ability (intelligence $r_g = -0.40$),
45 educational attainment (years of schooling $r_g = -0.46$) and reproductive traits (age at first birth $r_g = -$
46 0.58, father's age at death $r_g = -0.54$). Our findings provide a starting point towards identifying critical
47 biosocial risk mechanisms for the development of ASB.

48

49

50

51

52

53

54 **Main**

55 Antisocial behaviors (ASB) are disruptive acts characterized by covert and overt hostility and
56 violation of the rights and safety of others¹. The emotional, social, and economic costs incurred by
57 victims of antisocial behavior are far-reaching, ranging from victims' psychological trauma to reduced
58 productivity when victims miss work to costs incurred by taxpayers in order to staff and run a justice
59 system^{2,3}. ASB has been recognized not merely as a social problem, but also as a mental health
60 economic priority⁴. In addition of causing harm to others, those with ASB are themselves at elevated
61 risk of criminal convictions as well as mental health and substance abuse problems⁵. Given all this, it
62 is a research imperative to illuminate the mechanisms underlying the pathogenesis, emergence, and
63 persistence of ASB.

64 Toward this end, statistical genetic studies have consistently revealed the relevance of environmental
65 and genetic risk factors in the genesis of inter-individual differences in ASB. Family studies - mostly
66 conducted in samples of European ancestry - have demonstrated a considerable heritable component
67 for ASB, with estimates of approximately 50%⁶ across studies. The increasing availability of genome-
68 wide data along with data on dimensional ASB measures facilitates in building more advanced
69 explanatory models aimed at identifying trait-relevant genetic variants, that could serve as moderators
70 of socio-environmental factors and vice versa. Moreover, while heritability estimates can differ across
71 subtypes of ASB (e.g., significantly higher twin-based heritability estimates for aggressive forms
72 (65%) versus non-aggressive, rule-breaking forms (48%) of antisocial behavior⁷), these subtypes are
73 genetically correlated ($r_g = .38$)⁸.

74 *Measuring antisocial behaviour, a broad view*

75 Considering multiple forms of ASB together increases power of genetic analysis and may improve
76 our ability to detect new genetic variants. Here, we thus examine a broadly defined construct of
77 antisocial behaviors, an approach that has successful precedents. Large-scale genomic studies have
78 indicated substantial genetic overlap among psychiatric disorders⁹. A recent genome-wide meta-
79 analysis across eight neuropsychiatric disorders revealed extensive pleiotropic genetic effects (N =
80 232,964 cases and 494,162 controls)^{10,11}. The study found that 109 out of the total 146 contributing

81 loci were associated with at least two psychiatric disorders, suggesting broad liability to these
82 conditions. Moreover, the Externalizing Consortium recently conducted a multivariate analysis of
83 large-scale genome-wide association studies (GWAS) of seven externalizing-related phenotypes (N=
84 ~1.5 million) and found 579 genetic associations with a general liability to externalizing behavior¹².
85 Although these very large multivariate approaches are crucial in enhancing genetic discovery across
86 phenotypes, they do not detect all the genetic variation relevant to individual disorders. Since ASB is
87 a critical issue for psychiatry and for society, the present study uniquely focuses on (severe) forms of
88 ASB and persistence over the lifespan. To do so, we initiated the Broad Antisocial Behavior
89 Consortium (BroadABC), to perform large-scale meta-analytical genetic analyses, utilizing a broad
90 range of phenotypic ASB measures (e.g., conduct disorder symptoms, aggressive behavior, and
91 delinquency). In our first meta-analysis¹³, we demonstrated that effect sizes for SNPs with suggestive
92 evidence of association with ASB were small, as anticipated for most polygenic traits. Still, we found
93 that the collective effect across all of the included variants (typically referred to as ‘SNP heritability’)
94 explained roughly 5% of the total variation in ASB¹³, which is in line with meta-analyses of the
95 ACTION¹⁴ and EAGLE¹⁵ consortium.

96 To date, however, no previous GWAS meta-analysis targeting broad ASB detected SNPs or genes
97 that are well-replicated. The polygenic architecture of ASB underscores the importance of employing
98 very large samples to yield sufficient power to detect genetic loci of small effect size. Therefore, we
99 substantially boost statistical power by quadrupling the sample size and adding new cohorts to the
100 BroadABC consortium. Since ASB is a critical issue for psychiatry and for society, the present study
101 uniquely focuses on (severe) forms of ASB and persistence over the lifespan.

102 In our meta-analysis, we also include the results of a GWAS study of Disruptive Behavior Disorders
103 (DBDs) in the context of Attention-Deficit/Hyperactivity Disorder (ADHD), which identified three
104 genome-wide significant loci for DBDs¹⁶. The present study considers multiple measures of antisocial
105 behaviors in people with and without psychiatric diagnoses across 28 samples to reveal the genetic
106 underpinnings of ASB phenotypes typically studied in psychology, psychiatry, and criminology.
107 These larger samples allow well-powered genetic correlation analyses and improved polygenic risk

108 scores (PRS). Five independent cohorts (total N = 8,058) were employed to validate the ASB PRS in
109 different populations, at different developmental stages, and for different ASB phenotypes. Moreover,
110 we conducted a follow-up analysis of significant loci by using a mouse model of pathological
111 aggression. Since ASB is known to correlate phenotypically with an array of cognitive and health
112 problems¹⁷, we tested for genetic overlap between ASB and a range of other traits and disorders,
113 including anthropometric, cognitive, reproductive, neuropsychiatric, and smoking.

114 **Results**

115 **Meta-analysis on broad ASB identifies association with common variants in FOXP2**

116
117 After quality control and imputation to the Haplotype Reference Consortium or 1000 Genomes
118 Project reference panel (see **Online Methods**), 85,359 individuals from 28 cohorts and a maximum of
119 7,392,849 variants were available for analysis. We carried out a pooled-sex GWAS meta-analysis for
120 the broad ASB phenotype with METAL¹⁸ and found one genome-wide significant locus, on
121 chromosome 7 (chromosome band 7q31.1, **Fig. 1A, Supplementary Table 3**). The top lead SNP was
122 rs12536335 ($P = 6.32 \times 10^{-10}$; **Fig. 1B and 1C**), located in an intronic region upstream of one of the
123 transcriptional start-sites for the forkhead box protein P2 (*FOXP2*) gene^{19,20}. Consistent with this
124 finding, a gene-based association test carried out with MAGMA²¹, identified significant association
125 for *FOXP2* ($P = 7.43 \times 10^{-7}$, **Supplementary Note 3, Supplementary Figure 1, Supplementary**
126 **Table 6**). The *FOXP2* gene has been related to the development of speech and language²², yet is also
127 implicated in a wide range of other traits and diagnoses²³ (see **Fig. 1D**). MAGMA generalized gene-
128 set and tissue-specific gene-set analyses (sex-combined) yielded no significant gene-sets after
129 Bonferroni-correction for multiple testing. The top gene-set for generalized gene-set analysis was
130 activated NTRK2 signals through RAS signaling pathway, **Supplementary Table 7**, while the top
131 tissue-specific gene expression was the hypothalamus, **Supplementary Table 8**). We next ran sex-
132 specific GWAS meta-analyses. These analyses did not identify SNPs that reached genome-wide
133 significance (**Supplementary Tables 4 and 5**).

134

135 **Mouse model of pathological aggression**

136 Whole genome sequencing analysis of SNVs in aggressive antisocial BALB/cJ mice compared to
137 BALB/cByJ mice controls revealed differences between these lines located in introns of *Foxp2*
138 (rs241912422) and *Cntnap2* (rs212805467; rs50446478; rs260305923; rs242237534), a well-studied
139 neural target of this transcription factor.

140 **Heritability and Polygenic Scoring**

141 **SNP heritability**

142 To assess the proportion of variance in liability for broad ASB explained by all measured SNPs, we
143 computed the SNP-based heritability (h^2_{SNP}), which was estimated to be 8.3% (s.e. = 1.2%) by LD
144 score regression (LDSC)²⁴.

145

146

147

148

149

150

151

152

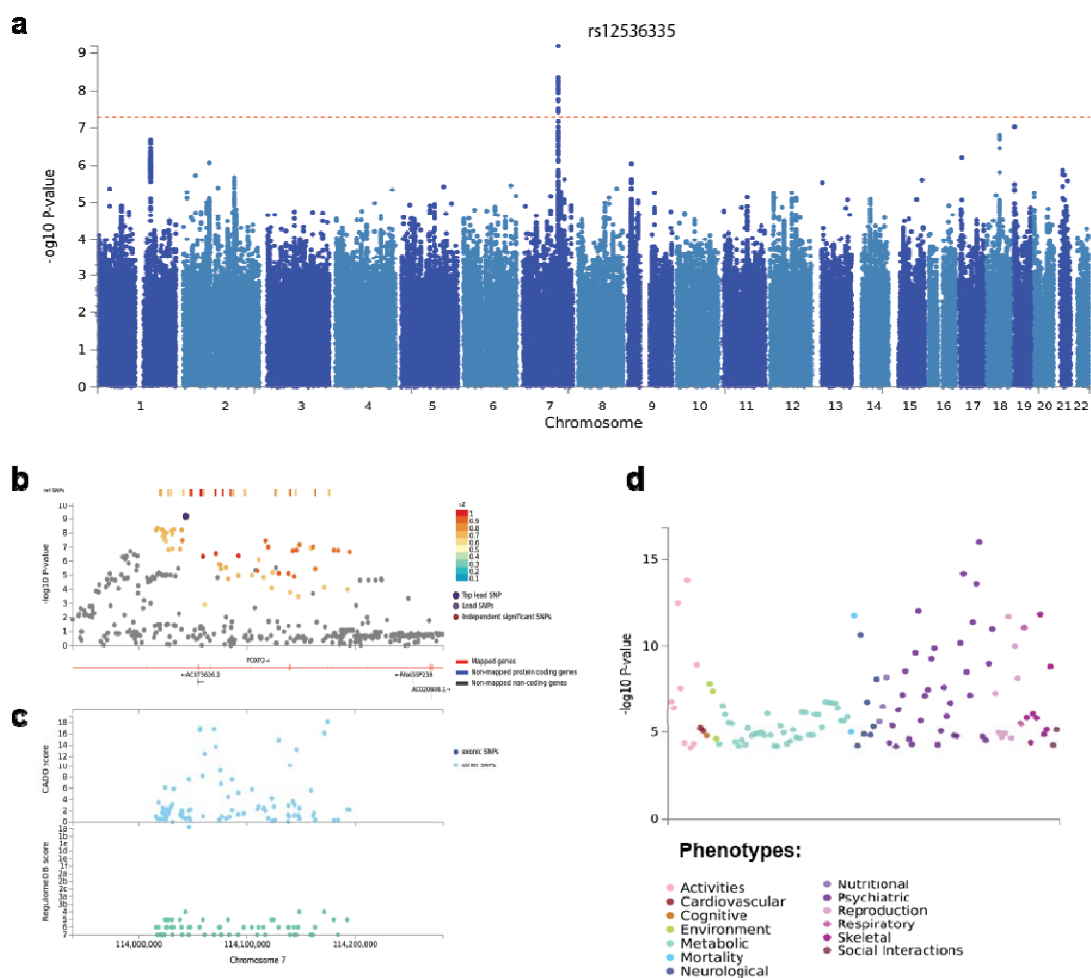
153

154

155

156

157 **Figure 1: SNP-based results from the GWAS meta-analysis of broad ASB.**



158 **Figure 1. A.** Manhattan plot of the GWAS meta-analysis ($N = 85,359$) of a broad antisocial behavior
159 phenotype, showing the negative log₁₀-transformed P value for each SNP. SNP two-sided P values from a
160 linear model were calculated using METAL¹⁸, weighting SNP associations by sample size. **B.** Regional
161 association plot around chromosome 7:114043159 with functional annotations of SNPs in LD of lead SNP
162 rs12536335 (shown in purple). The plot displays GWAS P-value plotted against its chromosomal position,
163 where colors represent linkage disequilibrium and r^2 values with the most significantly associated SNP. **C.** The
164 plot displays CADD scores (Combined Annotation Dependent Depletion) and RegulomeDB scores of these
165 SNPs. **D.** PheWAS plot showing the significance of associations of common variation in the *FOXP2* gene with
166 a wide range of traits and diagnoses based on MAGMA gene-based tests (with Bonferroni corrected P-value:
167 1.05e-5), as obtained from GWASAtlas (<https://atlas.ctglab.nl>).

169

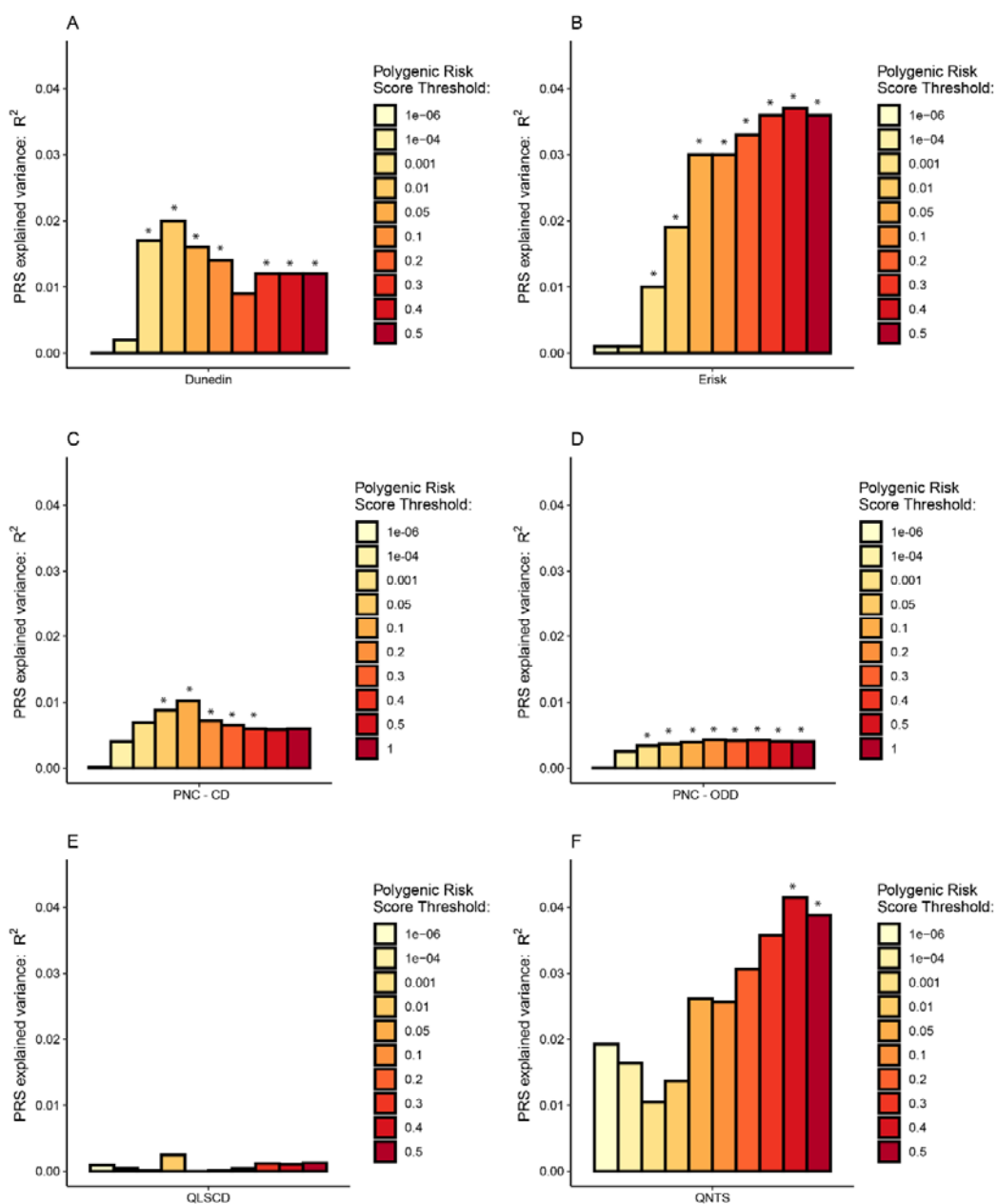
170

171

172

173

174 **Figure 2: Polygenic risk score (PRS) associations of broad ASB with six antisocial outcomes in**
 175 **five cohorts.**



176

177 **Figure 2.** Bar charts illustrating the proportion of variance (incremental R^2 , or ΔR^2) explained by the PRSs.
 178 PRSs are shown for broad ASB associated with childhood ASB in the Dunedin Longitudinal Study [A], with
 179 externalizing behavior in the E-Risk Study [B], with Conduct Disorder [C] and Oppositional Defiant Disorder
 180 [D] in the Philadelphia Neurodevelopmental Cohort Study, with ASB in the Quebec Longitudinal Study of
 181 Children's Development Study [E], and with time-aggregated ASB in the Quebec Newborn Twin Study [F].
 182 Asterisks (*) show statistical significance after applying a Bonferroni correction on the 22 tested phenotypes at
 183 $P < < 0.0023$.

184

185 **Polygenic Risk Scoring in five independent cohorts**

186 To assess how well the PRS derived from our ASB GWAS meta-analysis predicts other measures of
187 antisocial behavior, we carried out PRS analyses in five independent cohorts (Supplementary Note 7).

188 *Dunedin Longitudinal Study*

189 In New Zealand, participants were derived from the Dunedin Longitudinal Study²⁵ (N=1,037,
190 assessed 14 times from birth to age 45 years). We tested nine phenotypes and found significant
191 associations with the BroadABC-based PRS for two: childhood ASB and official-records of juvenile
192 convictions. Although not surviving Bonferroni adjustment, we found nominal significant ($P < 0.05$)
193 association with the BroadABC-based PRS for eight phenotypes. We did not find evidence for a PRS
194 association with partner violence. Lastly, we compared individuals grouped into the following four
195 distinct developmental trajectories of antisocial behavior using general growth mixture modeling: low
196 antisocial behavior across childhood through adulthood, childhood-limited antisocial behavior,
197 adolescent-onset antisocial behavior, and life-course persistent antisocial behavior²⁶. Individuals
198 following the life-course persistent (LCP) antisocial trajectory were characterized by the highest
199 levels of genetic risk (see Supplementary Figure 2); the nominally significant higher PRS of the LCP
200 trajectory group compared to the low ASB group ($P = 0.032$ and $P = 0.049$, for P-value thresholds
201 0.05 and 0.1 respectively) did not survive Bonferroni adjustment. For a full report of the findings in
202 the Dunedin cohort, see Supplementary Table 9 and Supplementary Note 8.

203 *Environmental Risk Longitudinal Twin Study (E-Risk)*

204 In England and Wales, participants were included from the E-Risk Study (N=2,232, assessed five
205 times from birth to age 18 years). We tested eight phenotypes and found significant associations for
206 seven. PRS analyses revealed significant associations with parent- and teacher-reported antisocial
207 behavior up to age 12 years, conduct disorder diagnosis up to age 12 years, with the externalizing
208 spectrum at age 18 years, and with official records of criminal convictions up to age 22 years. For a
209 full report of the findings in the E-risk Study, see Supplementary Table 10 and Supplementary Note 8.

210

211 *Philadelphia Neurodevelopmental Cohort (PNC)*

212 In the United States, participants were included from the PNC Study (N=4,201). We tested two
213 phenotypes and found significant associations for both. We found that higher PRS for ASB were
214 associated with symptom counts of both conduct disorder ($P < 0.0001$, $\Delta R^2=1.0\%$, Supplementary
215 Table 11) and oppositional defiant disorder ($P < 0.0001$, $\Delta R^2=0.4\%$, Supplementary Table 12).

216 *Quebec Longitudinal Study of Children's Development (QLSCD)*

217 In Canada, participants were included from the QLSCD study (N=599). We tested one phenotype and
218 did not find a significant association ($P > 0.05$, Supplementary Table 13) between PRS and the score
219 on a self-report questionnaire related to conduct disorder, delinquency, and broad antisocial behavior
220 in young adults (age range= 18-19 years).

221 *Quebec Newborn Twin Study (QNTS)*

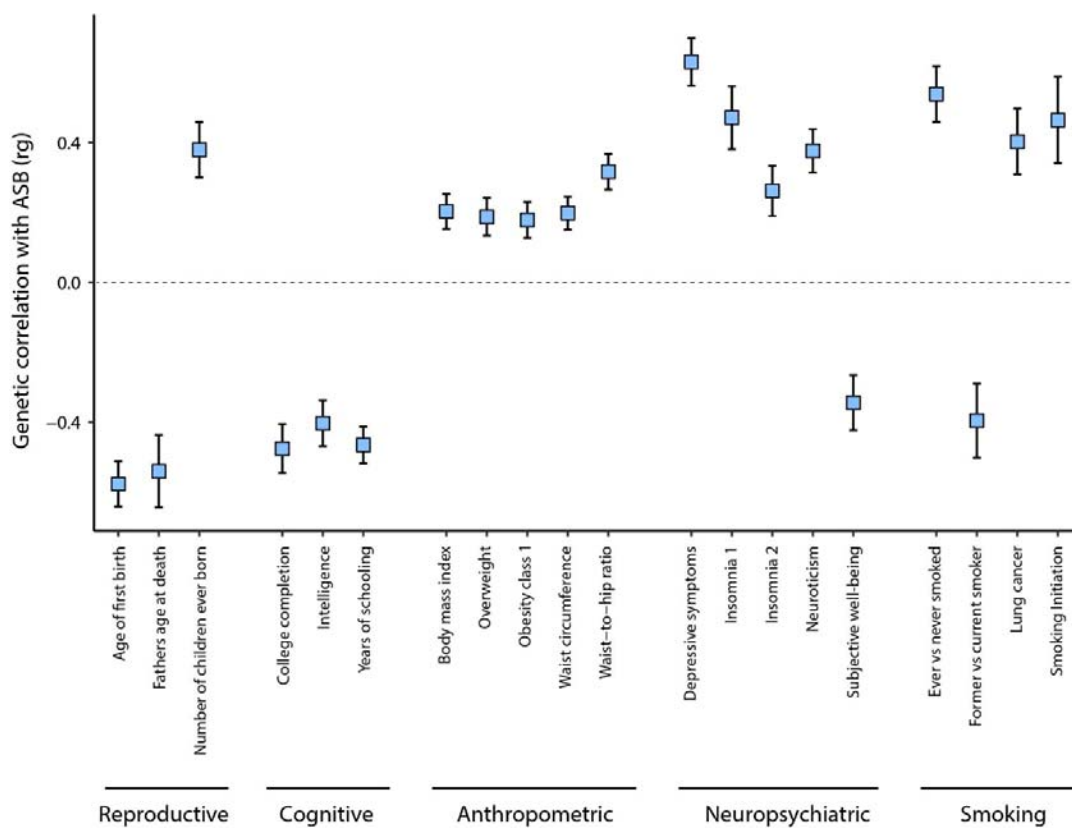
222 In Canada, participants were derived from the QNTS study (N=341). We tested two phenotypes and
223 found a significant association for one. We computed a factor score based upon five teacher-rated
224 assessments of ASB in youngsters during primary school (age range= 6-12 years). We found that
225 higher PRS were associated with a higher factor score of ASB ($P = 0.001$, for P-value thresholds .4,
226 adjusted $\Delta R^2=3.9\%$, Supplementary Table 14). We failed to find evidence for an association
227 between PRS and self-reported antisocial behavior in young adults ($P > 0.05$).

228 **Genetic correlations through LD score regression**

229 ASB is known to correlate with an array of problems¹⁷. To test whether these phenotypic associations
230 are also reflected in genetic correlations we performed analyses with LDSC in 68 traits and diagnoses
231 (Supplementary Table 15). We found strong correlations between ASB and reproductive traits (e.g.
232 younger age of first birth ($r_g = -0.58$, $s.e. = 0.06$, $P = 2.93 \times 10^{-15}$)), cognitive traits (e.g.
233 fewer years of schooling ($r_g = -0.49$, $s.e. = 0.06$, $P = 1.94 \times 10^{-10}$)), anthropometric traits
234 (e.g. increased waist-to-hip ratio ($r_g = 0.32$, $s.e. = 0.05$, $P = 5.59 \times 10^{-6}$)), neuropsychiatric traits

235 (e.g. more depressive symptoms ($rg = 0.63$, $s.e. = 0.07$, $P = 2.45 \times 10^{-16}$)) and smoking
236 related traits (e.g. ever smoked ($rg = 0.54$, $s.e. = 0.08$, $P = 1.48 \times 10^{-7}$)).

237 **Figure 3: Genetic correlations of traits and diseases that were significantly associated with ASB**



238

239 **Figure 3.** Significant genetic correlations of ASB with previously published results of other traits and diseases,
240 computed using cross-trait LD Score Regression in LDHub, Bonferroni-corrected P-value: 0.00074 (bars
241 represent 95% confidence intervals).

242

243

244

245

246

247

248

249 **Discussion**

250 Our GWAS meta-analysis of broad ASB in 85,359 individuals from population cohorts and those with
251 a clinical diagnosis related to ASB, revealed one novel associated locus on chromosome 7
252 (7:114043159, rs12536335), residing in the forkhead box P2 (*FOXP2*) gene. The lead SNP is
253 relatively proximal (~14kb upstream) to an important enhancer region located 330 kb downstream of
254 the first transcriptional start site (TSS1) of the gene²⁰. This SNP is also in the vicinity (~8kb upstream)
255 of a second transcriptional start site (TSS2) of *FOXP2* that can drive expression of alternative
256 transcripts. The *FOXP2* gene is expressed in sensory, limbic, and motor circuits of the brain, as well
257 as the lungs, heart, and gut²⁰. It encodes a transcription factor that acts as a regulator of numerous
258 target genes and has been implicated in multiple aspects of brain development (e.g. neuronal growth,
259 synaptic plasticity)²⁷. *FOXP2* was first identified two decades ago when rare heterozygous mutations
260 of the gene were linked to a monogenic disorder involving speech motor deficits, accompanied by
261 impairments in expressive and receptive language^{28,29}. Nevertheless, so far there is little evidence for a
262 role of common *FOXP2* variants in interindividual differences in language function^{30,31}. Thus, even
263 though earlier behavioral research^{32,33,34} has reported a link between language problems and ASB, we
264 should not over-interpret the *FOXP2* findings of the present study. Moreover, SNPs at this locus have
265 been associated, through GWAS, with a range of externalizing traits, including ADHD³⁵, cannabis use
266 disorder³⁶, and generalized risk tolerance³⁷. Given the involvement of SNPs at this locus in different
267 behavioral traits and diagnoses, and considering the small effect sizes, it is clear that the association of
268 *FOXP2* variation with ASB has limited explanatory value on its own, but could yield insights once
269 placed in broader context by future research.

270 In the present study we also compared the BALB/cJ strain, a mouse model of pathological aggression,
271 to BALB/cByJ controls, and found intronic variants in *Foxp2* and one of its downstream targets,
272 *Cntnap2*. Previous studies in human cellular models have shown that the protein encoded by *FOXP2*
273 can directly bind to regulatory regions in the *CNTNAP2* locus to repress its expression³⁸. Interestingly,

274 mice with cortical-specific knockout of *Foxp2* have been reported to show abnormalities in social
275 behaviors³⁹. Although these findings may indicate that the intronic SNVs are relevant to the behavioral
276 differences between the strains, further evidence is needed to show that the variants actually have
277 functional relevance for the mouse phenotype. Future studies may utilize complementary data
278 comparing gene expression in the two mouse lines or could investigate functional impact (e.g. do they
279 map to credible enhancer regions, are they likely to alter binding for transcription factors?) of the
280 SNVs identified.

281 In contrast with the previous BroadABC GWAS analyses, we did not find evidence for sex-specific
282 genetic effects in the present study. Although we did have access to sex-specific data in considerable
283 subsets (N = 22,322 males, N = 26,895 females), the power to detect new variants employing such
284 sample sizes is still limited. Compared to our previous study, we found that the variance explained in
285 independent samples by PRS based on the resulting summary statistics has substantially increased
286 from 0.21% to 3.9%. Essentially, we found consistent links of our ASB PRS with multiple antisocial
287 phenotypes at different developmental stages, from different reporting sources, and reflecting
288 measurements from different disciplines (psychology, psychiatry, criminology). These links were
289 found in individuals from New Zealand, Britain, the United States, and Canada, born 30 years apart.
290 We also show that our ASB PRS were more strongly associated with more severe and persistent types
291 of ASB.

292 Notwithstanding the increase of effect size of the PRS, and calculations yielding a more precise
293 estimate, the variance explained by the PRS was still relatively small, which was expected in light of
294 the low SNP heritability of 8.3%. Given the highly polygenic architecture of ASB, contributing SNPs
295 have low average effect sizes, thus leading to limited predictive power in independent samples. New
296 PRS methods along with further increasing sample sizes will likely further increase the amount of
297 variance accounted for by the PRS. Moreover, the association may be enhanced by improving the
298 quality of phenotype measurements, which is reflected by our PRS results demonstrating the most
299 robust association with high quality measurement of ASB (using a factor score based upon multiple
300 assessments). Aggregating data from measurements across ages, as opposed to the measures assessed

301 at a single time point, can lead to more reliable trait measures and to better prediction⁴⁰.
302 Phenotypically, adding more extreme ASB phenotypes to the GWAS meta-analysis might also lead to
303 more explained variance. Thus, future efforts of the BroadABC will continue to focus on more severe
304 forms of ASB and its persistence across the lifespan. Moreover, by considering genetically correlated
305 traits through multi-trait GWAS methods⁴¹ and multi-trait PRS methods⁴² it might be possible to boost
306 power for discovery through GWAS meta-analysis and PRS prediction. Lastly, a major limitation of
307 the present study is that our GWAS results are limited to individuals of European ancestry. This
308 Eurocentric bias may lead to more accurate predictions in individuals with European ancestry,
309 compared to non-Europeans, thus potentially increasing disparities in outcomes related to ASB^{43,44}.
310 To realize the full and equitable potential of polygenic risk, future genetic studies on ASB should also
311 include non-European samples.

312 Developmental criminological research findings, such as the influential developmental taxonomy
313 theory by Moffitt^{45,46}, have established the existence of distinctive offending patterns across the life-
314 course⁴⁷. These distinctive developmental trajectories of ASB are thought to have different underlying
315 etiological processes, with higher genetic influences for life-course-persistent offending as compared
316 to the more socially influenced adolescence-limited offending. Barnes and coworkers showed that the
317 heritability was not uniform across different offending groups, suggesting that the causal processes
318 may vary across offending patterns^{48,49}. In the present study we found a trend of higher PRS for ASB
319 showing a stronger association with the life-course-persistent trajectory of ASB as compared to the
320 low ASB group. The life-course-persistent trajectory is also known to be associated with the most
321 profound brain alterations and poorest brain health⁵⁰. These findings are important since they can
322 improve understanding of downstream neurobiological mechanisms relevant to the etiology of
323 antisocial development⁵⁰. Sufficiently powered future studies should thus aim to further elucidate the
324 genetic risk and protective factors that underlie different offending trajectories⁵¹.

325 Our genetic correlation analyses confirmed previously reported^{13,17,52} correlations between ASB and a
326 wide range of traits and diagnoses. Partial sharing of genetic effects does not necessarily represent
327 causal relationships, yet merely signifies the presence of potentially shared biology or other

328 mechanisms linking the conditions⁵³. Therefore, it is likely that there are common underlying genetic
329 factors increasing general vulnerability to psychopathologies. These comorbid effects are in line with
330 findings in the Dunedin Study demonstrating that life-course-persistent offenders are characterized by
331 several pathological risk factors, related to domains of parenting, neurocognitive development, and
332 temperament⁴⁶. This signifies the importance of investigating pleiotropy and considering the complex
333 etiology of the broader ASB phenotype. Large-scale collaborations, such as the BroadABC, will
334 facilitate the expansion of epidemiological studies capable of further exploring the interaction of
335 genetic risk and socio-environmental risks, and how these contribute to the multifaceted origin of
336 ASB.

337 **Methods**

338 **Samples**

339 The meta-analysis included 21 new discovery samples of the BroadABC with GWAS data on a
340 continuous measure of ASB, totaling 50,252 participants: The National Longitudinal Study of
341 Adolescent to Adult Health⁵⁴ (ADH), Avon Longitudinal Study of Parents and Children⁵⁵⁻⁵⁷
342 (ALSPAC), Brain Imaging Genetics⁵⁸ (BIG), CoLaus|PsyCoLaus⁵⁹, Collaborative Study on the
343 Genetics of Alcoholism⁶⁰ (COGA), Finnish Twin Cohort⁶¹ (FinnTwin), The Genetics of Sexuality and
344 Aggression⁶² (GSA), Minnesota Center for Twin and Family Research⁶³ (MCTFR), Phenomics and
345 Genomics Sample⁶⁴ (PAGES), eight samples of the QIMR Berghofer Medical Research Institute
346 (QIMR; 16Up project [16UP⁶⁵], Twenty-Five and Up Study [25UP⁶⁶], Genetics of Human Agency
347 [GHA⁶⁷], Prospective Imaging Study of Ageing [PISA⁶⁸], Semi-Structured Assessment for the
348 Genetics of Alcoholism SSAGA Phase 2 [SS2⁶⁹], Genetic Epidemiology of Pathological Gambling
349 [GA⁷⁰], Twin 89 Study [T89⁷¹], and Nicotine Study [NC⁷²]), Spit for Science⁷³ (S4S), two samples
350 (from different genotype platforms) of the Twin Early Development Study⁷⁴ (TEDS), and the
351 TRacking Adolescents' Individual Lives Survey⁷⁵ (TRAILS).

352 We complemented the above data with GWAS summary statistics on case-control data on disruptive
353 behavior disorders from the recently published Psychiatric Genetics Consortium/iPSYCH consortium

354 meta-analysis, which included data from seven cohorts (Cardiff sample, CHOP cohort, IMAGE-I &
355 IMAGE-II samples, Barcelona sample, Yale-Penn cohort, and the Danish iPSYCH cohort), totaling
356 3,802 cases and 31,305 controls¹⁶.

357 We observed a high genetic correlation between the 21 meta-analyzed BroadABC samples and the 7
358 Psychiatric Genetics Consortium/iPSYCH samples, with the ‘Effective N’ as weight ($r_g = 0.93$, $P =$
359 9.04×10^{-8}), indicating strong overlap of genetic effects. Hence, we continued with the combined 28
360 samples ($N = 85,359$) for all analyses.

361 All included studies were approved by local ethics committees, and informed consent was obtained
362 from all of the participants. All study participants were of European ancestry. Full details on
363 demographics, measurements, sample analysis, and quality control are provided in Supplementary
364 Table 1.

365 **Genome-wide association analysis and quality control of individual cohorts**

366 In all 28 discovery samples, genetic variants were imputed using the reference panel of the Haplotype
367 Reference Consortium (HRC) or the 1000G Phase 1 version 3 reference panel. The regression
368 analyses were adjusted for age at measurement, sex, and the first ten principal components. To
369 harmonize the imputation, data preparation, and genome-wide association (GWA) analyses, a specific
370 analysis protocol (Supplementary Note 1) was followed in the 18 BroadABC discovery samples.
371 Further details on the genotyping (platform and quality control criteria), imputation, and GWA
372 analyses for each cohort are provided in Supplementary Table 2.

373 Two semi-independent analysts (JJT & EU) performed stringent within-cohort quality control,
374 filtering out poor performing SNPs. SNPs were excluded if they met any of the following criteria:
375 study-specific minor allele frequency (MAF) corresponding to a minor allele count (MAC) < 100 ,
376 poor imputation quality ((INFO/R2) score < 0.6), and/or Hardy–Weinberg equilibrium
377 $P < 5 \times 10^{-6}$. Moreover, we excluded SNPs and indels that were ambiguous (A/T or C/G with
378 MAF > 0.4), duplicated, monomorphic, multiallelic, or reference-mismatched (Supplementary Note
379 2, Supplementary Table 17). Then, we visually inspected the distribution of the summary statistics by

380 creating quantile–quantile plots and Manhattan plots for the cleaned summary statistics from each
381 cohort (Supplementary Notes 4, 5 and 6). Discrepancies between the results files of the two semi-
382 independent analysts were examined and errors corrected.

383 **Meta-analyses on combined and sex-specific samples**

384 A meta-analysis of the GWAS results of the 28 discovery samples (N = 85,359) was performed
385 through fixed-effects meta-analysis in METAL, using SNP P-values weighted by sample size. After
386 combining all cleaned GWAS data files, meta-analysis results were filtered to exclude any variants
387 with $N \leq 30,000$. Consequently, we removed 2,134,049 SNPs, resulting in 7,392,849 SNPs
388 available for analysis. To investigate sex-specific genetic effects, we also ran the meta-analysis in the
389 datasets for which we had sex-specific data (N = 50,252). However, sex-specific SNP heritabilities, as
390 estimated with LD Score Regression, were small and non-significant (3.7% (s.e. = 2.2%) for males
391 and 1.0% (s.e. = 1.8%) for females). Due to the non-significant sex-specific heritability estimates, the
392 genetic correlation of male and female ASB could not be estimated reliably and no sex-specific
393 follow-up analyses were conducted.

394 **Whole-genome sequencing based on genetic differences between the BALB/c strains**

395 Through whole-genome sequencing, we identified single nucleotide variants that distinguish
396 aggressive BALB/cJ mice from control BALB/cByJ strains⁷⁶. Sequencing libraries were prepared
397 from high-quality genomic DNA using the TruSeq DNA PCR-Free kit (Illumina) and ultra-deep
398 whole genome sequencing (average 30X read-depth across the genome) was performed on a HiSeq X
399 Ten System (Illumina). We developed an efficient data processing and quality control pipeline.
400 Briefly, raw sequencing data underwent stringent quality control and was aligned to either the mm10
401 (BALB/cJ versus BALB/cByJ strain comparison). Isaac⁷⁷ was used to align reads and call single
402 nucleotide variations (SNVs). We excluded SNVs that were covered by less than 20 reads, and that
403 were not present in both animals from the same strain. SnpEff⁷⁸ was used to annotate SNVs and
404 explore functional effects on gene function. SNVs differing between the two strains were annotated to
405 a total of 1573 genes, which were subdivided into three different categories (intronic/exonic non-

406 coding and synonymous variants (1422 genes), untranslated regions (90 genes), missense mutations
407 and splicing variants (61 genes)).

408

409 **Polygenic Risk Score Analyses**

410 Polygenic risk scores (PRS) were created for ASB using all available SNPs of the discovery
411 dataset^{79,80}. PRS were computed as the weighted sum of the effect-coded alleles per individual. We
412 calculated the PRS for subjects of five independent datasets, selected for their detailed phenotypes
413 related to antisocial outcomes: (1) the Dunedin Study⁴⁰, (2) the E-risk study⁸¹, (3) the Philadelphia
414 Neurodevelopmental Cohort⁸², (4) the Quebec Longitudinal Study of Child Development⁸³, and (5)
415 the Quebec Newborn Twin Study⁸⁴. All individuals were of European ancestry. To maintain
416 uniformity across target cohorts, we adhered to the following parameters: Clumping was performed
417 by removing markers in linkage disequilibrium, utilizing the following thresholds: maximum $r^2 = 0.2$,
418 window size = 500 kb. We excluded variants within regions of long-range LD⁸⁵ (including the Major
419 Histocompatibility Complex, see Supplementary Table 16 for exact regions). Second generation
420 PLINK⁸⁶ was employed to construct PRS for each phenotype, at the following 10 thresholds:
421 $P < 1 \times 10^{-6}$, $P < 1 \times 10^{-4}$, $P < 1 \times 10^{-3}$, $P < 1 \times 10^{-2}$, $P < 0.05$, $P < 0.1$,
422 $P < 0.2$, $P < 0.3$, $P < 0.4$, $P < 0.5$. To correct for multiple testing, we applied a Bonferroni
423 correction on the 22 tested phenotypes ($\alpha = 0.00227$).

424 **Genetic correlation analysis**

425 To estimate the genetic correlation between ASB and a range of other phenotypes, we employed
426 Linkage Disequilibrium Score Regression (LDSC)²⁴ through the LD Hub web portal
427 (<http://ldsc.broadinstitute.org/ldhub/>)⁸⁷. We corrected for multiple testing by applying a Bonferroni
428 correction on the 68 tested genetic correlations ($\alpha = 0.0007$).

429

430

431

432

433

434 **Acknowledgements**

435 G.M-V. was supported by a Doctoral Research Scholarship from the FRQSC. M.B., I.O-M., and J-P
436 Gouin are supported by the Canada Research Chair Program. K.R. is supported by a Sir Henry
437 Wellcome Postdoctoral Fellowship. ADB and DD were supported by grants from the Lundbeck
438 Foundation (R102-A9118, R155-2014-1724 and R248-2017-2003), the EU FP7 Program (Grant No.
439 602805, “Aggressotype”) and H2020 Program (Grant No. 667302, “CoCA”), NIMH
440 (1U01MH109514-01. JL, AM, and KR acknowledge the following funders: Academy of Finland, the
441 Signe and Ane Gyllenberg foundation, Juho Vainio foundation, Yrjö Jahnsson foundation, Jalmari
442 and Rauha Ahokas foundation, Sigrid Juselius Foundation and The Finnish Society of Sciences and
443 Letters. DD is supported by NIH R01 AA015416 (Finnish Twin Study), P50 AA022537 (Alcohol
444 Research Center), R25 AA027402 (VCU GREAT), R34 AA027347 (Personalized Risk Assessment),
445 R01 AA028064 (Parental Marital Discord, PI: JS), and U10 AA008401 (COGA) from the National
446 Institute on Alcohol Abuse and Alcoholism (NIAAA), and by R01 DA050721 (Externalizing
447 Consortium) from the National Institute on Drug Abuse (NIDA). BF, MK, and NRM were also
448 supported by funding from the European Community’s Horizon 2020 Programme (H2020/2014 –
449 2020) under grant agreements n° 728018 (Eat2beNICE) and n° 847879 (PRIME). They also received
450 relevant funding from the Netherlands Organization for Scientific Research (NWO) for the Dutch
451 National Science Agenda NeurolabNL project (grant 400-17-602). HMS and MRM are members of
452 the Medical Research Council (MRC) Integrative Epidemiology Unit at the University of Bristol
453 (MC_UU_00011/7). This work is also supported by the NIHR Biomedical Research Centre at
454 University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views
455 expressed in this publication are those of the authors and not necessarily those of the NHS, the
456 National Institute for Health Research or the Department of Health and Social Care. AW has been

457 supported by funding from the European Union Seventh Framework Programme (FP7/2007-2013)
458 under grant agreement no. 602768 for the ACTION consortium. JK has been supported by the
459 Academy of Finland Academy professorship program (grants 265240 and 263278). LC-C was
460 supported by a QIMR Berghofer Research Fellowship. JJM was supported by a QIMR Berghofer
461 International PhD Scholarship. ML was funded by an NHMRC Boosting Dementia Leadership
462 Fellowship (APP1140441). SEM and NGM were funded by NHMRC investigator grants
463 (APP1172917 and APP1172990).

464 Additional acknowledgements for each study cohort are described in **Supplementary Table 1**.

465

466 **References**

467

- 468 1. Allen, J. J. & Anderson, C. A. Aggression and Violence: Definitions and Distinctions. in *The Wiley*
469 *Handbook of Violence and Aggression* 1–14 (American Cancer Society, 2017).
470 doi:10.1002/9781119057574.whbva001.
- 471 2. Rivenbark, J. G. *et al.* The high societal costs of childhood conduct problems: evidence from
472 administrative records up to age 38 in a longitudinal birth cohort. *Journal of Child Psychology and*
473 *Psychiatry* **59**, 703–710 (2018).
- 474 3. Brewin, C. R., Andrews, B., Rose, S. & Kirk, M. Acute stress disorder and posttraumatic stress
475 disorder in victims of violent crime. *Am J Psychiatry* **156**, 360–366 (1999).
- 476 4. Eme, R. Male Life-Course-Persistent Antisocial Behavior: The Most Important Pediatric Mental
477 Health Problem. *Archives of Pediatrics & Adolescent Medicine* **164**, 486–487 (2010).
- 478 5. Abram, K. M. *et al.* Comorbidity and continuity of psychiatric disorders in youth after detention: a
479 prospective longitudinal study. *JAMA Psychiatry* **72**, 84–93 (2015).
- 480 6. Polderman, T. J. C. *et al.* Meta-analysis of the heritability of human traits based on fifty years of
481 twin studies. *Nature Genetics* **47**, 702–709 (2015).

- 482 7. Burt, S. A. Are there meaningful etiological differences within antisocial behavior? Results of a
483 meta-analysis. *Clin Psychol Rev* **29**, 163–178 (2009).
- 484 8. Burt, S. A. & Klump, K. L. Etiological distinctions between aggressive and non-aggressive antisocial
485 behavior: results from a nuclear twin family model. *J Abnorm Child Psychol* **40**, 1059–1071 (2012).
- 486 9. Smoller, J. W. *et al.* Psychiatric genetics and the structure of psychopathology. *Molecular*
487 *Psychiatry* **24**, 409–420 (2019).
- 488 10. Lee, P. H. *et al.* Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight
489 Psychiatric Disorders. *Cell* **179**, 1469–1482.e11 (2019).
- 490 11. Abdellaoui, A., Smit, D. J. A., van den Brink, W., Denys, D. & Verweij, K. J. H. Genomic
491 relationships across psychiatric disorders including substance use disorders. *Drug Alcohol Depend*
492 **220**, 108535 (2021).
- 493 12. Linnér, R. K. *et al.* Multivariate genomic analysis of 1.5 million people identifies genes related
494 to addiction, antisocial behavior, and health. *bioRxiv* 2020.10.16.342501 (2020)
495 doi:10.1101/2020.10.16.342501.
- 496 13. Tielbeek, J. J. *et al.* Genome-Wide Association Studies of a Broad Spectrum of Antisocial
497 Behavior. *JAMA Psychiatry* **74**, 1242–1250 (2017).
- 498 14. Ip, H. *et al.* Genetic Association Study of Childhood Aggression across raters, instruments and
499 age. (2019). doi:10.1101/854927.
- 500 15. Pappa, I. *et al.* A genome-wide approach to children’s aggressive behavior: The EAGLE
501 consortium. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* **171**, 562–
502 572 (2016).
- 503 16. Demontis, D. *et al.* Risk variants and polygenic architecture of disruptive behavior disorders
504 in the context of attention-deficit/hyperactivity disorder. *Nature Communications* **12**, 576 (2021).
- 505 17. Tielbeek, J. J. & Boutwell, B. B. Exploring the Genomic Architectures of Health, Physical Traits
506 and Antisocial Behavioral Outcomes: A Brief Report. *Front Psychiatry* **11**, 539 (2020).

- 507 18. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide
508 association scans. *Bioinformatics* **26**, 2190–2191 (2010).
- 509 19. MacDermot, K. D. *et al.* Identification of FOXP2 Truncation as a Novel Cause of
510 Developmental Speech and Language Deficits. *Am J Hum Genet* **76**, 1074–1080 (2005).
- 511 20. Becker, M., Devanna, P., Fisher, S. E. & Vernes, S. C. Mapping of Human FOXP2 Enhancers
512 Reveals Complex Regulation. *Front Mol Neurosci* **11**, 47 (2018).
- 513 21. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: Generalized Gene-Set
514 Analysis of GWAS Data. *PLoS Comput Biol* **11**, (2015).
- 515 22. den Hoed, J. & Fisher, S. E. Genetic pathways involved in human speech disorders. *Current*
516 *Opinion in Genetics & Development* **65**, 103–111 (2020).
- 517 23. Watanabe, K. *et al.* A global overview of pleiotropy and genetic architecture in complex
518 traits. *Nat Genet* **51**, 1339–1348 (2019).
- 519 24. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in
520 genome-wide association studies. *Nature Genetics* **47**, 291–295 (2015).
- 521 25. Poulton, R., Moffitt, T. E. & Silva, P. A. The Dunedin Multidisciplinary Health and
522 Development Study: overview of the first 40 years, with an eye to the future. *Soc Psychiatry*
523 *Psychiatr Epidemiol* **50**, 679–693 (2015).
- 524 26. Odgers, C. L. *et al.* Female and male antisocial trajectories: from childhood origins to adult
525 outcomes. *Dev Psychopathol* **20**, 673–716 (2008).
- 526 27. den Hoed, J., Devaraju, K. & Fisher, S. E. Molecular networks of the FOXP2 transcription
527 factor in the brain. *EMBO Rep* **22**, e52803 (2021).
- 528 28. Lai, C. S. L., Fisher, S. E., Hurst, J. A., Vargha-Khadem, F. & Monaco, A. P. A forkhead-domain
529 gene is mutated in a severe speech and language disorder. *Nature* **413**, 519–523 (2001).
- 530 29. Lai, C. S. L., Gerrelli, D., Monaco, A. P., Fisher, S. E. & Copp, A. J. FOXP2 expression during
531 brain development coincides with adult sites of pathology in a severe speech and language
532 disorder. *Brain* **126**, 2455–2462 (2003).

- 533 30. Uddén, J. *et al.* Toward Robust Functional Neuroimaging Genetics of Cognition. *J Neurosci*
534 **39**, 8778–8787 (2019).
- 535 31. Deriziotis, P. & Fisher, S. E. Speech and Language: Translating the Genome. *Trends Genet* **33**,
536 642–656 (2017).
- 537 32. Warr-Leeper, G., Wright, N. A. & Mack, A. Language disabilities of antisocial boys in
538 residential treatment. *Behavioral Disorders* **19**, 159–169 (1994).
- 539 33. Cohen, N. J. *et al.* Language, social cognitive processing, and behavioral characteristics of
540 psychiatrically disturbed children with previously identified and unsuspected language
541 impairments. *J Child Psychol Psychiatry* **39**, 853–864 (1998).
- 542 34. Brownlie, E. *et al.* Early Language Impairment and Young Adult Delinquent and Aggressive
543 Behavior. *Journal of abnormal child psychology* **32**, 453–67 (2004).
- 544 35. Demontis, D. *et al.* Discovery of the first genome-wide significant risk loci for attention
545 deficit/hyperactivity disorder. *Nat Genet* **51**, 63–75 (2019).
- 546 36. A large-scale genome-wide association study meta-analysis of cannabis use disorder - The
547 Lancet Psychiatry. [https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366\(20\)30339-](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30339-4/fulltext)
548 [4/fulltext](https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(20)30339-4/fulltext).
- 549 37. Karlsson Linnér, R. *et al.* Genome-wide association analyses of risk tolerance and risky
550 behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. *Nat*
551 *Genet* **51**, 245–257 (2019).
- 552 38. Vernes, S. C. *et al.* A functional genetic link between distinct developmental language
553 disorders. *N Engl J Med* **359**, 2337–2345 (2008).
- 554 39. Medvedeva, V. P. *et al.* Altered social behavior in mice carrying a cortical Foxp2 deletion.
555 *Human Molecular Genetics* **28**, 701–717 (2019).
- 556 40. Caspi, A. *et al.* Longitudinal Assessment of Mental Health Disorders and Comorbidities Across
557 4 Decades Among Participants in the Dunedin Birth Cohort Study. *JAMA Netw Open* **3**, (2020).

- 558 41. Turley, P. *et al.* Multi-trait analysis of genome-wide association summary statistics using
559 MTAG. *Nature Genetics* **50**, 229–237 (2018).
- 560 42. Maier, R. M. *et al.* Improving genetic prediction by leveraging genetic correlations among
561 human diseases and traits. *Nature Communications* **9**, 989 (2018).
- 562 43. Whose genomics? *Nat Hum Behav* **3**, 409–410 (2019).
- 563 44. Martin, A. R. *et al.* Clinical use of current polygenic risk scores may exacerbate health
564 disparities. *Nat Genet* **51**, 584–591 (2019).
- 565 45. Moffitt, T. E. *Adolescence-limited and Life-course-persistent Antisocial Behavior: A*
566 *Developmental Taxonomy*. (1993).
- 567 46. Moffitt, T. E. Male antisocial behaviour in adolescence and beyond. *Nature Human*
568 *Behaviour* **2**, 177–186 (2018).
- 569 47. Jennings, W. G. & Reingle, J. M. On the number and shape of developmental/life-course
570 violence, aggression, and delinquency trajectories: A state-of-the-art review. *Journal of Criminal*
571 *Justice* **40**, 472–489 (2012).
- 572 48. Barnes, J. C., BEAVER, K. & Boutwell, B. Examining the genetic underpinnings of Moffitt’s
573 developmental taxonomy: A behavioral genetic analysis. *Criminology* **49**, 923–954 (2011).
- 574 49. Motz, R. T. *et al.* Does contact with the justice system deter or promote future delinquency?
575 Results from a longitudinal study of British adolescent twins. *Criminology* **58**, 307–335 (2020).
- 576 50. Carlisi, C. O. *et al.* Associations between life-course-persistent antisocial behaviour and brain
577 structure in a population-representative longitudinal birth cohort. *The Lancet Psychiatry* **7**, 245–
578 253 (2020).
- 579 51. Wertz, J. *et al.* Genetics and Crime: Integrating New Genomic Discoveries Into Psychological
580 Research About Antisocial Behavior. *Psychol Sci* **29**, 791–803 (2018).
- 581 52. Tielbeek, J. J. *et al.* Exploring the genetic correlations of antisocial behaviour and life history
582 traits. *BJPsych Open* **4**, 467–470 (2018).

- 583 53. Martin, J., Taylor, M. J. & Lichtenstein, P. Assessing the evidence for shared genetic risks
584 across psychiatric disorders and traits. *Psychol Med* **48**, 1759–1774 (2018).
- 585 54. Harris, K. M. *et al.* Cohort Profile: The National Longitudinal Study of Adolescent to Adult
586 Health (Add Health). *International Journal of Epidemiology* **48**, 1415–1415k (2019).
- 587 55. Boyd, A. *et al.* Cohort Profile: the 'children of the 90s'--the index offspring of the Avon
588 Longitudinal Study of Parents and Children. *Int J Epidemiol* **42**, 111–127 (2013).
- 589 56. Northstone, K. *et al.* The Avon Longitudinal Study of Parents and Children (ALSPAC): an
590 update on the enrolled sample of index children in 2019. *Wellcome Open Res* **4**, (2019).
- 591 57. Fraser, A. *et al.* Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC
592 mothers cohort. *Int J Epidemiol* **42**, 97–110 (2013).
- 593 58. Franke, B. *et al.* Genetic variation in CACNA1C, a gene associated with bipolar disorder,
594 influences brainstem rather than gray matter volume in healthy individuals. *Biol Psychiatry* **68**,
595 586–588 (2010).
- 596 59. Preisig, M. *et al.* The PsyCoLaus study: methodology and characteristics of the sample of a
597 population-based survey on psychiatric disorders and their association with genetic and
598 cardiovascular risk factors. *BMC Psychiatry* **9**, 9 (2009).
- 599 60. The Collaborative Study on the Genetics of Alcoholism. *Alcohol Health Res World* **19**, 228–
600 236 (1995).
- 601 61. Kaprio, J. The Finnish Twin Cohort Study: an update. *Twin Res Hum Genet* **16**, 157–162
602 (2013).
- 603 62. Johansson, A. *et al.* The Genetics of Sexuality and Aggression (GSA) twin samples in Finland.
604 *Twin Res Hum Genet* **16**, 150–156 (2013).
- 605 63. Miller, M. B. *et al.* The Minnesota Center for Twin and Family Research Genome-Wide
606 Association Study. *Twin Res Hum Genet* **15**, 767–774 (2012).
- 607 64. Rujescu, D. *et al.* Genome-Wide Association Study in Vestibular Neuritis: Involvement of the
608 Host Factor for HSV-1 Replication. *Front Neurol* **9**, 591 (2018).

- 609 65. Mitchell, B. L. *et al.* 16Up: Outline of a Study Investigating Wellbeing and Information and
610 Communication Technology Use in Adolescent Twins. *Twin Res Hum Genet* **23**, 345–357 (2020).
- 611 66. Mitchell, B. L. *et al.* Twenty-Five and Up (25Up) Study: A New Wave of the Brisbane
612 Longitudinal Twin Study. *Twin Res Hum Genet* **22**, 154–163 (2019).
- 613 67. Morosoli, J. J., Colodro-Conde, L., Barlow, F. K. & Medland, S. E. Investigating perceived
614 heritability of mental health disorders and attitudes toward genetic testing in the United States,
615 United Kingdom, and Australia. *Am J Med Genet B Neuropsychiatr Genet* (2021)
616 doi:10.1002/ajmg.b.32875.
- 617 68. Lupton, M. K. *et al.* A prospective cohort study of prodromal Alzheimer’s disease:
618 Prospective Imaging Study of Ageing: Genes, Brain and Behaviour (PISA). *Neuroimage Clin* **29**,
619 102527 (2021).
- 620 69. Madden, P. A. *et al.* Nicotine withdrawal in women. *Addiction* **92**, 889–902 (1997).
- 621 70. Slutske, W. S. *et al.* The Australian Twin Study of Gambling (OZ-GAM): Rationale, Sample
622 Description, Predictors of Participation, and a First Look at Sources of Individual Differences in
623 Gambling Involvement. *Twin Research and Human Genetics* **12**, 63–78 (2009).
- 624 71. Knopik, V. S. *et al.* Genetic effects on alcohol dependence risk: re-evaluating the importance
625 of psychiatric and other heritable risk factors. *Psychol Med* **34**, 1519–1530 (2004).
- 626 72. Saccone, S. F. *et al.* Genetic Linkage to Chromosome 22q12 for a Heavy-Smoking
627 Quantitative Trait in Two Independent Samples. *Am J Hum Genet* **80**, 856–866 (2007).
- 628 73. Dick, D. M. *et al.* Spit for Science: launching a longitudinal study of genetic and
629 environmental influences on substance use and emotional health at a large US university. *Front*
630 *Genet* **5**, 47 (2014).
- 631 74. McAra, L. & McVie, S. Youth crime and justice: Key messages from the Edinburgh Study of
632 Youth Transitions and Crime. *Criminology & Criminal Justice* **10**, 179–209 (2010).
- 633 75. Oldehinkel, A. J. *et al.* Cohort Profile Update: the TRacking Adolescents’ Individual Lives
634 Survey (TRAILS). *Int J Epidemiol* **44**, 76–76n (2015).

- 635 76. Jager, A. *et al.* Cortical control of aggression: GABA signalling in the anterior cingulate cortex.
636 *Eur Neuropsychopharmacol* **30**, 5–16 (2020).
- 637 77. Raczy, C. *et al.* Isaac: ultra-fast whole-genome secondary analysis on Illumina sequencing
638 platforms. *Bioinformatics* **29**, 2041–2043 (2013).
- 639 78. Cingolani, P. *et al.* A program for annotating and predicting the effects of single nucleotide
640 polymorphisms, SnpEff. *Fly (Austin)* **6**, 80–92 (2012).
- 641 79. Choi, S. W., Mak, T. S.-H. & O’Reilly, P. F. Tutorial: a guide to performing polygenic risk score
642 analyses. *Nature Protocols* **15**, 2759–2772 (2020).
- 643 80. Wray, N. R. *et al.* From Basic Science to Clinical Application of Polygenic Risk Scores: A
644 Primer. *JAMA Psychiatry* (2020) doi:10.1001/jamapsychiatry.2020.3049.
- 645 81. Wertz, J. *et al.* From Childhood Conduct Problems to Poor Functioning at Age 18 Years:
646 Examining Explanations in a Longitudinal Cohort Study. *J Am Acad Child Adolesc Psychiatry* **57**, 54-
647 60.e4 (2018).
- 648 82. Satterthwaite, T. D. *et al.* The Philadelphia Neurodevelopmental Cohort: A publicly available
649 resource for the study of normal and abnormal brain development in youth. *Neuroimage* **124**,
650 1115–1119 (2016).
- 651 83. Orri, M. *et al.* Cohort Profile: Quebec Longitudinal Study of Child Development (QLSCD). *Soc*
652 *Psychiatry Psychiatr Epidemiol* **56**, 883–894 (2021).
- 653 84. Boivin, M. *et al.* The Quebec Newborn Twin Study at 21. *Twin Res Hum Genet* **22**, 475–481
654 (2019).
- 655 85. Price, A. L. *et al.* Long-Range LD Can Confound Genome Scans in Admixed Populations. *Am J*
656 *Hum Genet* **83**, 132–135 (2008).
- 657 86. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer
658 datasets. *Gigascience* **4**, 7 (2015).

659 87. Zheng, J. *et al.* LD Hub: a centralized database and web interface to perform LD score
660 regression that maximizes the potential of summary level GWAS data for SNP heritability and
661 genetic correlation analysis. *Bioinformatics* **33**, 272–279 (2017).
662