



Heritability Estimation of Cognitive Phenotypes in the ABCD Study[®] Using Mixed Models

Diana M. Smith^{1,2,3} · Robert Loughnan⁴ · Naomi P. Friedman⁵ · Pravesh Parekh⁶ · Oleksandr Frei^{6,7} · Wesley K. Thompson⁸ · Ole A. Andreassen⁶ · Michael Neale⁹ · Terry L. Jernigan^{2,10,11,12} · Anders M. Dale^{3,10,11,12,13}

Received: 17 October 2022 / Accepted: 15 March 2023 / Published online: 7 April 2023
© The Author(s) 2023

Abstract

Twin and family studies have historically aimed to partition phenotypic variance into components corresponding to additive genetic effects (*A*), common environment (*C*), and unique environment (*E*). Here we present the ACE Model and several extensions in the Adolescent Brain Cognitive DevelopmentSM Study (ABCD Study[®]), employed using the new Fast Efficient Mixed Effects Analysis (FEMA) package. In the twin sub-sample ($n=924$; 462 twin pairs), heritability estimates were similar to those reported by prior studies for height (twin heritability = 0.86) and cognition (twin heritability between 0.00 and 0.61), respectively. Incorporating SNP-derived genetic relatedness and using the full ABCD Study[®] sample ($n=9,742$) led to narrower confidence intervals for all parameter estimates. By leveraging the sparse clustering method used by FEMA to handle genetic relatedness only for participants within families, we were able to take advantage of the diverse distribution of genetic relatedness within the ABCD Study[®] sample.

Keywords Heritability · Twin studies · Mixed models · Cognition · Height · Random effects

Introduction

For over a century, researchers have relied on variance partitioning as a statistical method for estimating heritability (Carey 2003). Historically, twin studies provided an avenue by which researchers could model the variance of a given

phenotype as comprised of distinct components: e.g., additive genetic effects (*A*), common environmental effects (*C*), and unique environmental effects (*E*, also including error or unmodeled unexplained variance; Martin and Eaves 1977; Neale and Maes 2004). Specifically, in a linear mixed-effect (LME) regression model,

✉ Diana M. Smith
d9smith@health.ucsd.edu

¹ Neurosciences Graduate Program, University of California San Diego, La Jolla, CA, USA

² Center for Human Development, University of California, San Diego, La Jolla, CA, USA

³ Center for Multimodal Imaging and Genetics, San Diego School of Medicine, University of California, La Jolla, CA, USA

⁴ Population Neuroscience and Genetics Lab, University of California, San Diego, La Jolla, CA, USA

⁵ Institute for Behavioral Genetics, Department of Psychology and Neuroscience, University of Colorado Boulder, Boulder, CO, USA

⁶ NORMENT, Division of Mental Health and Addiction, Oslo University Hospital & Institute of Clinical Medicine, University of Oslo, Oslo, Norway

⁷ Centre for Bioinformatics, Department of Informatics, University of Oslo, Oslo, Norway

⁸ Center for Population Neuroscience and Genetics, Laureate Institute for Brain Research, Tulsa, OK, USA

⁹ Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, USA

¹⁰ Department of Cognitive Science, University of California, San Diego, La Jolla, CA, USA

¹¹ Department of Radiology, University of California, San Diego School of Medicine, La Jolla, CA, USA

¹² Department of Psychiatry, University of California, San Diego School of Medicine, La Jolla, CA, USA

¹³ Department of Neuroscience, University of California, San Diego School of Medicine, La Jolla, CA, USA

$$y_{ij} = \mu + x_{ij}\beta + A_{ij} + C_{ij} + E_{ij} \quad (1)$$

where y_{ij} is the trait value of individual j in family i ; μ is the overall mean; x_{ij} denotes a vector of covariates; and A_{ij} , C_{ij} , E_{ij} represent latent additive genetic, common environmental and unique environmental random effects (ACE model), respectively. For longitudinal datasets in which participants are followed over time, the LME is also the recommended analysis that takes into account the random effect of subject (Pinheiro 2014), e.g.:

$$y_{ij} = \mu + x_{ij}\beta + A_{ij} + C_{ij} + S_{ij} + E_{ij} \quad (2)$$

where S_{ij} is the random effect of subject (e.g., subject ID), and the vector of covariates x_{ij} typically includes a fixed effect of time (e.g., age). In this way, the longitudinal LME assumes a linear combination of fixed and random effects to model the trajectory of the phenotype of interest over time.

Although the ACE model has often been implemented using structural equation model (SEM) software such as *OpenMx* (Neale et al. 2016), the SEM representation is mathematically equivalent to the LME regression model shown in Eq. 1 (Neale and Maes 2004; Visscher et al. 2004; McArdle and Prescott 2005). Indeed, prior applications of the ACE framework have been implemented using LMEs from R and Stata packages (Rabe-Hesketh et al. 2008) as well as SAS (Wang et al. 2011). For studies that incorporate extended family designs with several random effects, Visscher and colleagues (2004) recommended implementation using a LME approach, though SEM methods also exist to model complex family structure (Truett et al. 1994; Keller et al. 2009).

With recent advances in genomic sequencing, there has been an influx of methods that use measured genetic data rather than inferred genetic similarity from twin status. For example, genome-wide complex trait analysis (GCTA; Yang et al. 2011) was developed to incorporate a pairwise genetic relatedness matrix (GRM) between individuals using information from single nucleotide polymorphisms (SNPs). Twin studies have subsequently been adapted to incorporate empirical measures of genetic relatedness (Kirkpatrick et al. 2021). However, incorporating a matrix of pairwise relatedness values for each set of participants leads to an increase in the computational time when estimating these model parameters. Various subsequent adaptations have been developed to increase the processing speed of GCTA software (Ge et al. 2015) and to incorporate effects of maternal and/or paternal genotype on the traits within GCTA (Eaves et al. 2014; Qiao et al. 2020; Eilertsen et al. 2021).

Comparison of heritability estimates derived from non-twin versus twin analyses have found that non-twin studies consistently yield lower heritability estimates, an example

of the so-called “missing heritability” in genetics research (Kim et al. 2015). Some researchers have suggested that this phenomenon may be due, in part, to inflated twin heritability estimates; for example, due to dominant genetic variation which might be masked by shared environment in twin and family studies (Chen et al. 2015). Indeed, twin and family studies have developed several ways of parsing “common environment”, including using geospatial location information (Heckerman et al. 2016; Fan et al. 2018) and adding a random effect of twin status (T) when including twins and full siblings in the same study (Zyphur et al. 2013). It should also be noted that “SNP heritability” is a “narrow heritability” that only takes into account the additive genetic effects, and can be an underestimation of true heritability depending on SNP coverage. For example, estimates of SNP heritability tend to increase as SNP coverage increases from 300,000 SNPs to whole genome sequencing, and as rarer genetic variants are included (Wainschein et al. 2022).

The Adolescent Brain Cognitive DevelopmentSM Study (ABCD Study[®]) provides a particularly appealing dataset for the estimation of heritability, not only due to its population sampling framework, large sample size, and longitudinal design, but also because it contains an embedded sub-sample of 840 pairs of same-sex twins recruited through birth registries at four sites (Iacono et al. 2018). The overall sample is thus enriched for genetic relatedness, with families that include siblings, half siblings, dizygotic (DZ) twins, and monozygotic (MZ) twins. The ABCD Study[®] data therefore requires the application of modeling approaches that take repeated measures, family structure, and relatedness into account.

In this study we implemented modeling strategies that account for family structure and pairwise genetic relatedness using the recently developed Fast Efficient Mixed Effects Analysis (FEMA; Fan et al. 2021). We used FEMA to model participants nested within families, where random effects such as genetic relatedness were taken into account for each pair of subjects within a family, and set to zero for individuals who are not in the same family (Fan et al. 2021). For longitudinal data FEMA also allows inclusion of the random effect of subjects, which is a common practice for repeated-measures designs (Pinheiro 2014). FEMA provides a flexible platform for users to specify a wide array of fixed and random effects, which makes it a useful tool for modeling variance components in the ABCD Study[®]. The ABCD Study[®] Data Analysis, Informatics & Resource Center (DAIRC) intends to incorporate FEMA into the Data Exploration and Analysis Portal (DEAP) so that investigators can easily specify and run LMEs through this online platform. This paper is therefore intended to serve as a reference point for users who are examining random effects estimates on behavioral phenotypes using FEMA.

We first compared the basic ACE model implemented in *FEMA* versus *OpenMx* (Neale et al. 2016). Next, we tested the effect of including SNP-derived genetic relatedness (using genotype array data) compared to estimating relatedness based on kinship (i.e., 1.0 for MZ twins, 0.5 for DZ twins and full siblings). We then progressively expanded our sample size, first going from “twins only” to the full ABCD Study[®] baseline sample (including non-twin siblings and singletons), and finally to the full sample across multiple timepoints. We compared model estimates for the commonly used *A*, *C*, and *E* components, as well as a subject-level component (*S*) in the longitudinal data, and the twin component (*T*), which captured the variance attributable to variance in the common environment of twin pairs. In addition, we explored the change in model estimates and model fit when adjusting for specific fixed effect covariates, and when excluding the twin sub-sample.

Methods

Sample

The ABCD Study[®] is a longitudinal cohort of 11,880 adolescents beginning when participants were aged 9–11 years, with annual visits to assess mental and physical health (Volkow et al. 2018). The study sample spans 21 data acquisition sites and includes participants from demographically diverse backgrounds such that the sample demographics approximate the demographics of the United States (Garavan et al. 2018). The sample includes many siblings as well as a twin sub-sample consisting of 840 pairs of same-sex

twins recruited from state birth registries at four sites (Garavan et al. 2018). Exclusion criteria for participation in the ABCD Study[®] were: (1) lack of English proficiency in the child; (2) the presence of severe sensory, neurological, medical or intellectual limitations that would inhibit the child’s ability to comply with the study protocol; (3) an inability to complete an MRI scan at baseline. The study protocols were approved by the University of California, San Diego Institutional Review Board. Parent/caregiver permission and child assent were obtained from each participant. The data used in this study were obtained from ABCD Study[®] data release 4.0.

Statistical analyses were conducted on a sample that included a total of 13,984 observations from 9,742 unique participants across two timepoints (the baseline and year 2 visits). The twin sub-sample used in this study consisted of 462 pairs of twins with complete data (258 DZ pairs, 204 MZ pairs; total $N=924$). Observations were included in the final sample if the participant had complete data across sociodemographic factors (household income, highest parental education), available genetic data (to provide ancestry information using the top 10 principal components), and the phenotypes of interest. Table 1 shows the baseline demographics of the full sample as well as the twin sub-sample. Compared to the full sample, the twin sub-sample had a higher percentage of parents with bachelor’s degrees or above (67.3% compared to 61.8% in the full sample), and household income was shifted higher (52.7% with income over \$100,000 compared to 42.0% in the full sample).

Measures

Phenotypes of Interest

For the present study, we included height as a phenotype of interest due to its common use in twin and family studies (Silventoinen et al. 2003), as well as the availability of larger genetic studies from samples of unrelated participants (Yengo et al. 2022). Several cognitive phenotypes were included from the NIH toolbox cognition battery (Gershon et al. 2013): specifically, we analyzed the raw composite scores measuring fluid and crystallized intelligence, which have been validated against gold-standard measures of cognition (Akshoomoff et al. 2013; Heaton et al. 2014). We also included the uncorrected scores from the flanker task, picture sequence memory task, list sorting memory task, pattern comparison processing speed, dimensional change card sort task (components of fluid cognition); and the oral reading recognition task and picture vocabulary task (components of crystallized cognition). In addition to the NIH Toolbox, we included the matrix reasoning test from the Wechsler Intelligence Scales for Children (WISC-V; Wechsler 2014),

Table 1 Sample information at baseline. All samples include complete cases only. †Full sample included 241 pairs with SNP-derived relatedness > 0.9, implying 350 DZ pairs and 241 MZ pairs. ††Twin sub-sample included 258 DZ pairs and 204 MZ pairs

	Full sample	Twin sub-sample
N	8239	924
Number of families	7136	462
Number of twin pairs	591 [†]	462 ^{††}
Number of triplet pairs	8	0
Age (months; mean (SD))	118.94 (7.55)	121.79 (6.61)
Parental Education (%)		
< HS Diploma	320 (3.9)	18 (1.9)
HS Diploma/GED	680 (8.3)	38 (4.1)
Some College	2151 (26.1)	246 (26.6)
Bachelor	2196 (26.7)	308 (33.3)
Post Graduate Degree	2892 (35.1)	314 (34.0)
Household Income (%)		
< \$50,000	2404 (29.2)	170 (18.4)
>= \$50,000 & < \$100,000	2374 (28.8)	267 (28.9)
>= \$100,000	3461 (42.0)	487 (52.7)

the total percent correct from the Little Man visuospatial processing task (Acker 1982), and the total number of items correctly recalled across the five learning trials of the Rey Auditory Verbal Learning Task (RAVLT; Schmidt 1996). See Extended Methods for a complete description of each phenotype of interest including data collection procedures.

Covariates

Unless otherwise specified, models were run on data that was pre-residualized for age and sex only, in keeping with common practice for twin studies (Neale and Maes 2004). In models that included pre-residualization for additional covariates, these were chosen based on common practices in cognitive and behavioral research, and included recruitment site, parental education, household income, and the first ten genetic principal components.

Genetic Principal Components and Genetic Relatedness

Methods for collecting genetic data have been described in detail elsewhere (Uban et al. 2018). Briefly, a saliva sample was collected at the baseline visit, as well as a blood sample from twin pairs. The Smokescreen™ Genotyping array (Baurley et al. 2016) was used to assay over 300,000 SNPs. Resulting genotyped and imputed SNPs were used for principal components derivation as well as genetic relatedness calculation.

The genetic principal components were calculated using PC-AiR (Conomos et al. 2015). PC-AiR was designed for robust population structure inference in the presence of known or cryptic relatedness. Briefly, PC-AiR captures ancestry information that is not confounded by relatedness by finding a set of unrelated individuals in the sample that have the highest divergent ancestry and computes the PCs in this set; the remaining related individuals are then projected into this space. This method has been recommended by the Population Architecture through Genomics and Environment Consortium (Wojcik et al. 2019), which is principally concerned with conducting genetic studies in diverse ancestry populations.

PC-AiR was run on using the default suggested parameters from the GENESIS package (Gogarten et al. 2019). We used non-imputed SNPs passing quality control (516,598 variants and 11,389 individuals). Using the computed kinship matrix, PC-Air was then run on a pruned set of 158,103 SNPs, which resulted in 8,005 unrelated individuals from which PCs were derived – leaving 3,384 related individuals being projected onto this space.

We then computed a GRM using PC-Relate (Conomos et al. 2016). PC-Relate aims to compute a GRM that is independent from ancestry effects as derived from PC-AiR.

PC-Relate was run on the same pruned set of SNPs described above using the first two PCs computed from PC-Air.

Data Analysis

Pre-residualization

We used R version 3.6.3 for data processing. After obtaining the sample of complete cases for all variables, phenotypes were pre-residualized for age and sex using the *lm* function. For certain models (see Table 2), we additionally included the following covariates during this residualization step: site, parental education, income, and the first ten genetic principal components. The purpose of pre-residualization was to ensure that both FEMA and *OpenMx* implementations were fitting random effects to the same data. Because our models only fit random effects, and because FEMA implements an unbiased estimation of total variance, the FEMA implementation was therefore mathematically equivalent to *OpenMx*.

Previous work has found evidence for a practice effect in some of the cognitive measures from the ABCD Study® (Anokhin et al. 2022). Therefore, in models that included data from baseline and year 2, we included a “practice effect” as a dummy variable in the pre-residualization step. This variable was equal to 0 if the observation was the first instance of data for that participant (i.e., all participants had 0 at baseline), and 1 if the participants were providing data for the second time at the year 2 visit. Most participants ($N=4242$, 76.19%) had a value of 1 at the year 2 visit.

Model Specification

We ran a series of models, described in Table 2. For each model, we specified whether genetic relatedness was “SNP-derived” (calculated using PC-AiR and PC-Relate; Conomos et al. 2015; Conomos et al. 2016) or “kinship-derived”. For kinship-derived relatedness, we used the zygosity data from the twin sub-sample to assign a value of 1 for MZ twins, 0.5 for DZ twins, and 0.5 for all other siblings (under the assumption that there are only full siblings within a family).

Since each phenotype was pre-residualized, we only needed to estimate the random effects components in each LME run within FEMA and *OpenMx*. These included an effect of family ID (common environment, C), additive effect of genetic relatedness (A), subject (S), twin status (T , calculated by creating a variable “pregnancy ID” that was shared by any two individuals with the same family ID and same birth date), and unique environment/unexplained variance (E).

Table 2 List of model specifications. GRM = genetic relatedness matrix (derived from SNP data or kinship data); N_{obs} = number of observations; SNP = single nucleotide polymorphism; Y2 = year 2 follow-up visit. All models pre-residualized for age and sex; when specified, “all covariates” includes these as well as site, parental education, household income, and first ten genetic principal components. Samples correspond to sample information listed in Table 1. Random effects: A = additive genetic relatedness, C = common environment, S = subject, T = twin status (shared pregnancy ID), E = unexplained variance / error

Model	Sample	Timepoints	N_{obs}	GRM values	Covariates	Random Effects
Model 1	Twin	Baseline	924	Kinship	Age and sex	A, C, E
Model 2	Twin	Baseline	924	SNP	Age and sex	A, C, E
Model 3	Full	Baseline	8239	SNP	Age and sex	A, C, E
Model 4	Full	Baseline	8239	SNP	Age and sex	A, C, T, E
Model 5	Full	Baseline and Y2	13,984	SNP	Age and sex	A, C, E
Model 6	Full	Baseline and Y2	13,984	SNP	Age and sex	A, C, S, E
Model 7	Full	Baseline	8239	Kinship	Age and sex	A, C, E
Model 8	Full	Baseline	8239	Kinship	Age and sex	A, C, T, E
Model 9	Full	Baseline and Y2	13,984	Kinship	Age and sex	A, C, S, E
Model 10	Twin	Baseline	924	Kinship	All covariates	A, C, E
Model 11	Twin	Baseline	924	SNP	All covariates	A, C, E
Model 12	Full	Baseline	8239	SNP	All covariates	A, C, E
Model 13	Full	Baseline and Y2	13,984	SNP	All covariates	A, C, S, E
Model 14	Full	Baseline and Y2	13,984	SNP	Age and sex	A, C, S, E
Model 15	Full minus twins	Baseline and Y2	11,835	SNP	Age and sex	A, C, S, E

OpenMx

We first ran an ACE model in the baseline twin sample, using the *OpenMx* package in R (package version 2.20.6; Neale et al. 2016). We elected to use *OpenMx* as the comparison software due to its widespread use in twin and family studies to estimate heritability. We chose to use the restricted maximum likelihood (REML) estimator within *OpenMx*, which differs from ML estimators by (a) using an unbiased estimation to calculate total variance, and (b) first estimating the random effects iteratively and then estimating the fixed effects coefficients, as opposed to alternating estimation of variances and fixed effects. However, due to the preresidualization step described above, in our models we solely estimated random effects, such that the REML estimator in *OpenMx* provided a good comparison for FEMA (a ML estimator that uses an unbiased estimation of total variance). We ran *OpenMx* using R version 3.6.3., using the default SLSQP optimizer. Because data were preresidualized for age and sex, we did not fit any additional covariates. *OpenMx* provides likelihood-based confidence intervals by default (Neale and Miller 1997) which we used to compare with the likelihood-based confidence intervals calculated in FEMA.

Fast Efficient Mixed Effects Analysis (FEMA)

FEMA was developed for the efficient implementation of mass univariate LMEs in high-dimensional data (e.g., brain imaging phenotypes; Fan et al. 2021). Whereas the original version of FEMA used a method of moments estimator for increased computational efficiency, we modified the package to allow the user to select a ML estimator. When users specify ML as the estimator, FEMA arrives at parameter estimates by minimizing the log likelihood function specified in *FEMA_loglik*. An updated version of FEMA, including the relevant code, is available at the time of this publication (https://github.com/cmig-research-group/cmig_tools). Because FEMA uses an unbiased estimation of total variance, and we were only fitting random effects and not fixed effects, the estimates from the FEMA implementation of ML regression were predicted to be mathematically equivalent to the REML estimator used in *OpenMx*. To run FEMA, we passed a design matrix (the design matrix was “empty” because we were not fitting any fixed effects) as well as a file containing a matrix of (SNP- or kinship-derived) genetic relatedness values. FEMA then used a nested random effects design to create a sparse relatedness matrix, in which the relatedness values for all participants not assigned the same family ID was set to zero. For all models we reported the random effects variances as a percent of the total variance in the residualized phenotype that was explained by

variance in the random effect of interest. As a result, for a given model, the variance component estimates sum to 1 (representing 100% of the variance in the residualized phenotype). For ease of interpretation and comparison to previous literature, in this paper the term “heritability estimate” refers to the percent of residualized phenotypic variance that is explained by variance in genetic relatedness, i.e., variance explained by variance in A .

Confidence Interval Calculation

To generate 95% confidence intervals around parameter estimates, we used the *mxCI* function within *OpenMx*. The likelihood-based confidence intervals returned using *mxCI* are obtained by increasing or decreasing the value of each parameter until the -2 log likelihood of the model increases by an amount corresponding to the requested interval. The implementation of likelihood-based confidence intervals has been described in detail by Neale and Miller (1997).

FEMA used the same profile likelihood method to calculate confidence intervals (see Spratt 2000). Code for calculating confidence intervals is available within the *FEMA_fit* function on the publicly available GitHub repository. Briefly, *FEMA_fit* calculates a log likelihood threshold corresponding to the requested confidence interval, then solves a quadratic equation that describes the change in likelihood as a function of change in parameter value. The solution to this equation is applied to the parameter value of interest to achieve the specified confidence interval. Differences between FEMA and *OpenMx* confidence interval calculation are likely to be due to small differences in the specific implementations used.

Model Comparison

For comparing two models that used identical samples, we calculated the Akaike Information Criterion (AIC) as (Akaike 1974):

$$AIC = (-2)\ln(\text{likelihood}) + 2k \quad (2)$$

where k represents the number of model parameters. Therefore, the difference in AIC between two models (ΔAIC) can be calculated as:

$$\Delta AIC = -2(\Delta LL) + 2(\Delta k) \quad (3)$$

where ΔLL represents the difference in log likelihood between the two models and Δk represents the difference in the number of parameters between the two models. In models that have the same level of complexity ($\Delta k = 0$), the ΔAIC is equal to $-2(\Delta LL)$. We chose to use the AIC as opposed

to the likelihood ratio test statistic for model comparison because several comparisons were not between nested models.

Results

ACE Model (Model 1) in FEMA Versus *OpenMx*

A summary of heritability estimates (i.e., the A random effects) from all models is provided in Supplementary Table 1. To compare model estimates between *OpenMx* and FEMA, we fit the same ACE model in each, using the same sample of 462 complete twin pairs from the twin subsample (i.e., pairs in which each twin had complete data for all phenotypes). Figure 1 shows a comparison of the two results as well as the parameter estimates using FEMA. The difference in heritability estimates between the two software packages was less than 0.001 for all phenotypes. On comparing these models (Fig. 1B), we found that the difference in AIC was less than 0.05 for all phenotypes, indicating that there was no difference in the model fit. Because the model estimates and model fits were practically the same, we concluded that the two implementations were indeed mathematically equivalent, and therefore elected to use the LME implementation in FEMA for all further analyses.

Effect of Including Measured Genetic Relatedness (Model 2)

To test whether variance component estimates differ when including SNP- versus kinship-derived genetic relatedness, we fit two versions of the ACE model in the baseline twin sample. Model 1 (the ACE model described above, implemented in FEMA) used a matrix of kinship-derived relatedness values (1.0 for MZ twins and 0.5 for DZ twins) whereas Model 2 used a matrix of SNP-derived relatedness values.

The models provided equivalent heritability estimates, with differences in A estimates ranging from -0.01 (Little Man Task) to 0.03 (pattern comparison; Fig. 2A). On inspecting the differences in the AIC between the two models, we found that using SNP-derived GRM led to small improvements in the overall model fit. This improvement was most pronounced for height ($\Delta AIC = -1.04$) but less so for the cognitive phenotypes (Fig. 2B). Random effects variance component estimates are presented in Fig. 2C; overall, using SNP-derived GRM did not lead to dramatically different parameter estimates than using kinship-derived GRM.

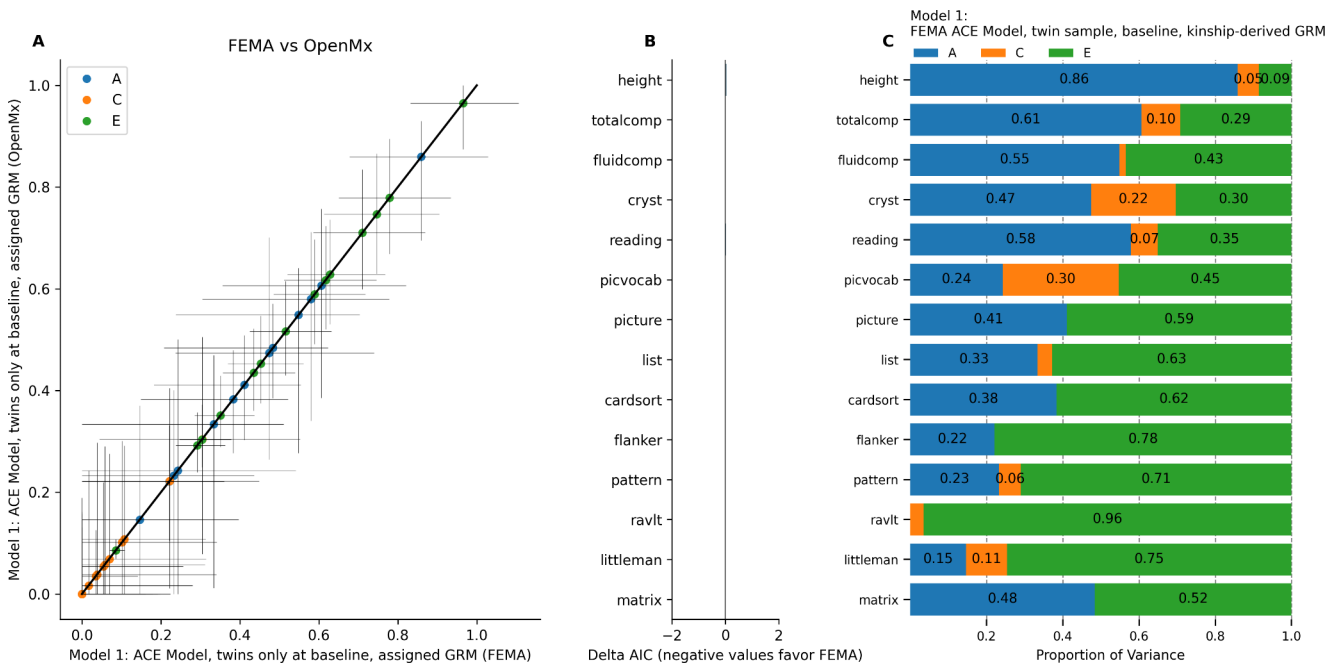


Fig. 1 ACE Model (Model 1) in FEMA versus OpenMx, twin sub-sample at baseline. (A) Comparison of model estimates. Horizontal error bars represent confidence interval calculated in FEMA; vertical error bars represent confidence intervals calculated in OpenMx. (B) Difference in Akaike Information Criterion in FEMA versus in OpenMx. (C) Random effects estimates from FEMA.

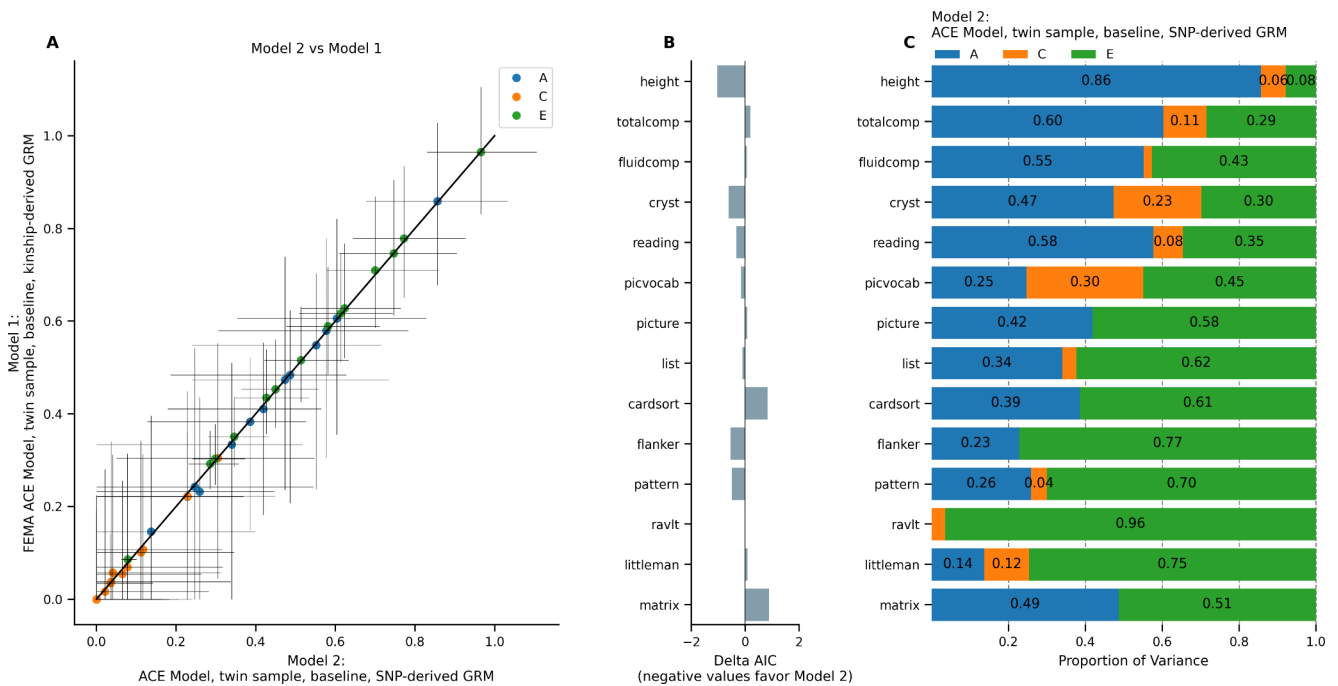


Fig. 2 ACE Model using kinship-derived (Model 1) versus SNP-derived GRM (Model 2), twin sub-sample at baseline. (A) Comparison of model estimates. Horizontal error bars represent confidence interval calculated in Model 2; vertical error bars represent confidence intervals calculated in Model 1. (B) Difference in Akaike Information Criterion in Model 2 versus in Model 1. (C) Random effects estimates from Model 2.

Effect of Increased Sample size (Model 3)

To examine how the variance component estimates in the twin sample ($n=924$) differ from the full ABCD Study® baseline sample ($n=8,239$), we next compared the ACE model in these two groups. Model 2 (from previous analysis) and Model 3 both used the SNP-derived GRM values and included *A*, *C*, and *E* random effects. The two models are therefore equivalent except for the much larger sample fit in Model 3. As described in Methods, the sparse clustering method within FEMA ignored the genetic relatedness among individuals with different family IDs. In practice, this meant that the sample of 8,239 unique subjects at baseline was clustered into 7,136 families, and genetic relatedness values were only used for individuals within families.

Figure 3 shows the estimates from Model 3 and their comparison to Model 2. The increased sample size led to smaller confidence intervals for most random effects estimates calculated in Model 3 (Fig. 3A). The changes in heritability estimates ranged from -0.31 (NIH Toolbox Fluid Cognition) to $+0.04$ (height). The estimated total variance was larger in Model 3 for most phenotypes (Fig. 3B), with the largest increase in variance in total composite cognition (24.36% increase in total variance), crystallized cognition (23.76% increase), and oral reading recognition (24.08% increase). Because the two models were fit to different samples, it was not possible to directly compare their AIC model fit from the likelihood statistics. Figure 3 C shows

the random effects variances from Model 3; results indicate that the total variance in the full sample was larger than that in the twin sample, and using the full sample led to smaller estimates of *A* and larger estimates of *C* compared to the twin sample.

Adding a Twin Random Effect (Model 4)

Given that the full sample analysis included singletons, half siblings, and adopted siblings, as well as twins and triplets, we next tested whether the addition of a random effect of twin status (*T*) led to a change in parameter estimates. We calculated a “pregnancy ID” that was shared by individuals who had the same family ID and the same birth date. We then used this “pregnancy ID” to code for the *T* random effect in an ACTE Model (Model 4). Supplementary Fig. 1 shows the model estimates from Model 4 as well as a comparison to Model 3; the two models are equivalent with the exception of the *T* random effect.

For most phenotypes, the addition of the *T* random effect did not lead to a change in parameter estimates (i.e., *T* was estimated to be 0). The largest change in parameter estimates was in matrix reasoning (heritability estimate decreased by 0.05, *T* estimated at 0.05; Supplementary Fig. 1A). Model comparison found that the difference in the AIC was at or near 2.0 for all phenotypes except for the RAVLT ($\Delta AIC=1.68$) and matrix reasoning ($\Delta AIC=1.35$). Because the AIC was calculated as -2ALL plus double the difference

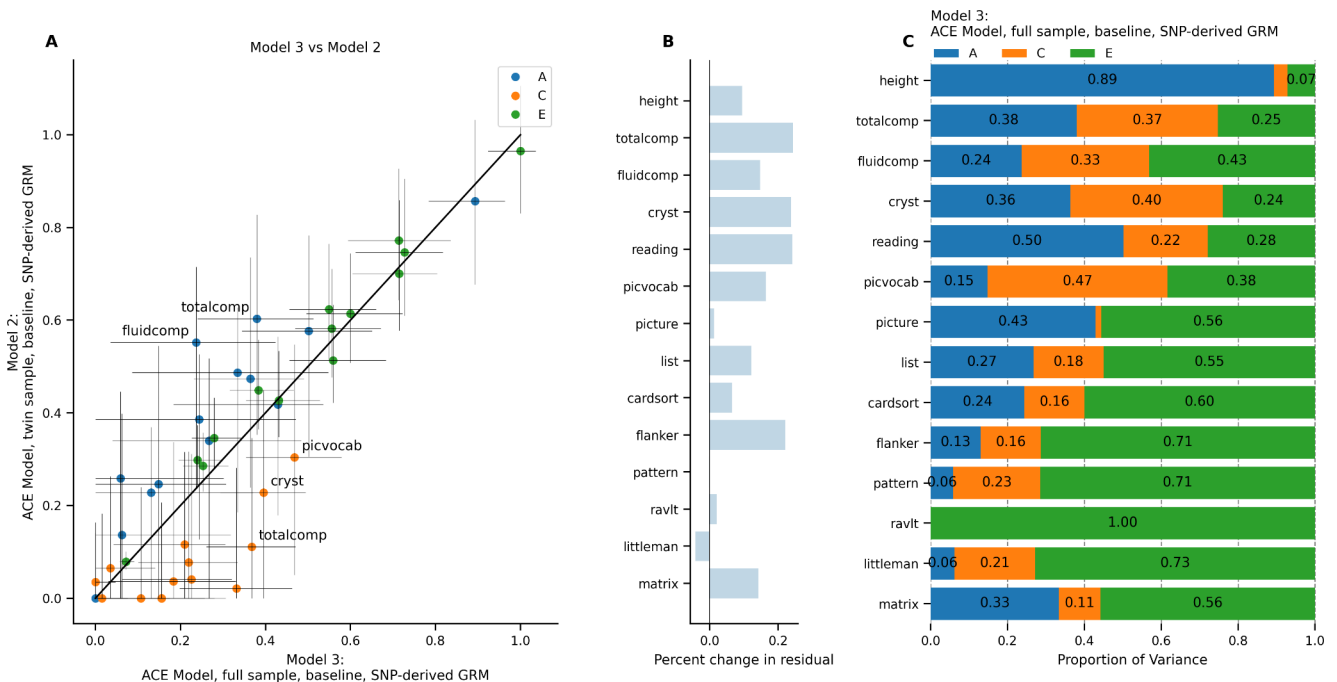


Fig. 3 ACE Model using full sample (Model 3) compared to twin subsample (Model 2) at baseline. (A) Comparison of model estimates. Horizontal error bars represent confidence interval calculated in Model

3; vertical error bars represent confidence intervals calculated in Model 2. (B) Difference in total residual variance in Model 3 versus in Model 2. (C) Random effects estimates from Model 3.

in model parameters (Eq. 3), the consistent values of 2.0 reflect that the $-2\Delta LL$ statistic was approximately 0 before the penalization for the additional parameter in Model 4 (Supplementary Fig. 1B). The random effects variances for Model 4 are shown in Supplementary Fig. 1C. Results indicate that T did not explain residual variance above and beyond the inclusion of A and C (matrix reasoning being a notable exception to this pattern).

Incorporation of Two Timepoints (Model 5, 6)

To compare the difference between cross-sectional and longitudinal samples, we next moved from examining the full sample at baseline (Model 3) to the full sample at baseline and Year 2 (Model 5). Models 3 and 5 were equivalent except for the difference in sample size (i.e., Model 5 did not account for nesting of data within subjects, in order to directly assess this effect in Model 6). Because not all phenotypes were available at the Year 2 visit, models that included baseline and Year 2 data only included pattern comparison processing speed, flanker task performance, picture sequence memory, picture vocabulary, oral reading recognition, crystallized cognition, RAVLT, Little Man Task, and height. To account for nesting of multiple visits within subjects, we added a random effect of subject (S) in Model 6. Figure 4 shows the change in random effects variances moving from Model 3 to Model 5 and from Model 5 to Model 6.

Adding the second visit led to overall increases in the heritability estimates for the cognitive phenotypes, with changes ranging from -0.06 (Little Man Task) to $+0.40$ (pattern comparison; Fig. 4A). Conversely, the heritability estimate for height decreased by 0.18 . Expanding from the full sample at baseline to the full sample at baseline and Year 2 led to an increase in the total residual variance for several phenotypes; the most notable increase was in the Little Man Task (7928% increase in total residual variance). Adding the random effect of subject led to minimal change (<0.02) in the heritability estimate for height, Little Man Task, and RAVLT, but a decrease in heritability estimates across the other cognitive phenotypes (changes ranging from -0.19 to -0.05) compared to estimates from Model 5. The total difference in heritability estimates going from Model 3 to Model 6 ranged from -0.18 (height) to $+0.22$ (pattern comparison; Fig. 4D).

Model comparison between Model 5 and Model 6 found that the model was substantially improved for crystallized cognition ($\Delta AIC = -5.19$), oral reading recognition ($\Delta AIC = -7.45$), picture vocabulary ($\Delta AIC = -5.61$), flanker ($\Delta AIC = -11.33$), and pattern comparison ($\Delta AIC = -25.60$). However, the difference in the fit was smaller for height ($\Delta AIC = +2.00$), picture sequence memory ($\Delta AIC = +0.89$),

the RAVLT ($\Delta AIC = +1.72$), and the Little Man Task ($\Delta AIC = +2.00$; Fig. 4E). Figure 4 C and 4 F show the random effects variances from Model 5 and Model 6. Overall, the increased sample size led to increased total residual variance and narrower confidence intervals, increases in heritability estimates for cognitive phenotypes, and a decrease in the heritability estimate for height, compared to the baseline only sample.

Effect of Using kinship-derived Genetic Relatedness in Large Samples (Model 7–9)

For the next set of models, we aimed to approximate a cohort study design in which genetic data were not available, to examine whether model estimates using several thousand subjects (Models 3,4,6) changed in the absence of SNP data. We used a matrix of kinship-derived genetic relatedness (assigning 1.0 for MZ twins from the twin sub-sample, and 0.5 for DZ twins from the twin sub-sample and all other individuals in the same family). The kinship-derived relatedness value therefore assumed that all non-twins in the same family, as well as twins who were not part of the twin sub-sample, were full siblings.

Figure 5 compares the ACSE longitudinal model with an equivalent model that used kinship-derived genetic relatedness. Supplementary Fig. 2 shows the same question of kinship-derived versus SNP-derived relatedness applied to Models 3 and 4. Overall, the random effects estimates were largely unchanged with the use of kinship-derived GRM, with the largest changes in the ACSE model occurring in flanker ($\Delta A = 0.09$) and pattern comparison ($\Delta A = -0.07$; Fig. 5A, Supplementary Fig. 2A,D). Model comparison using ΔAIC found that the ACSE model using SNP-derived GRM had better model fit for height ($\Delta AIC = -36.36$), crystallized cognition ($\Delta AIC = -17.59$), oral reading recognition ($\Delta AIC = -19.45$), picture vocabulary ($\Delta AIC = -8.75$), and pattern comparison ($\Delta AIC = -8.84$) compared to the model using kinship-derived GRM; the difference in model fit was less pronounced for picture sequence memory ($\Delta AIC = +0.46$) and flanker ($\Delta AIC = +0.45$; Fig. 5B, Supplementary Fig. 2B,E). Figure 5 C and Supplementary Fig. 2C and 2 F show the random effects variances for models using kinship-derived genetic relatedness; results indicate that using SNP-derived versus kinship-derived GRM led to small changes in heritability estimates, though model fit was better with SNP-derived GRM.

Residualizing for Additional Covariates (Models 10–13)

While it is common in twin and family analyses to include only age and sex as fixed effects, behavioral scientists often

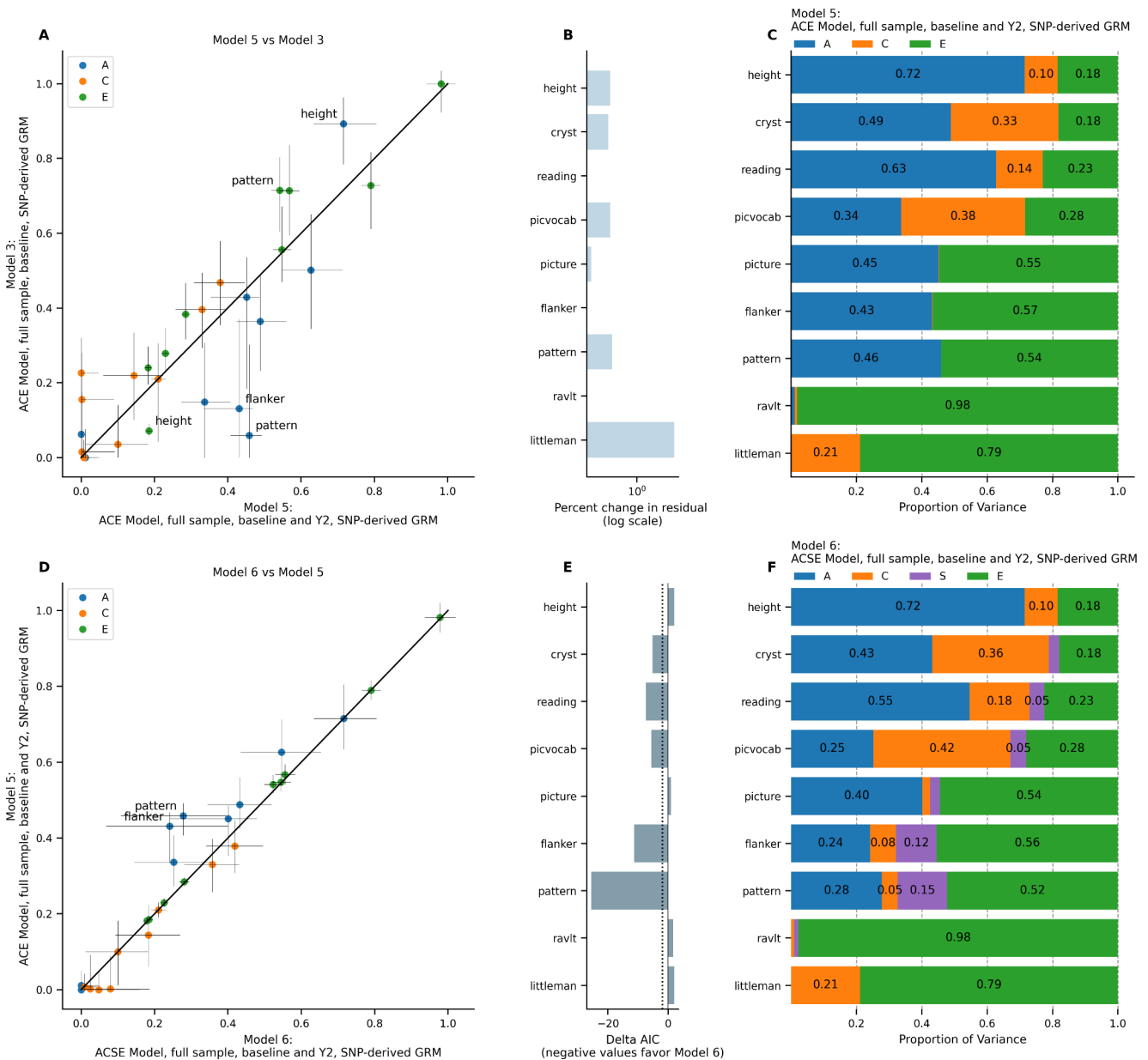


Fig. 4 ACE and ACSE Model in full sample, baseline only (Model 3) versus baseline + year 2 (Models 5 and 6). (A) Comparison of estimates from Model 5 versus Model 3. Horizontal error bars represent confidence interval calculated in Model 5; vertical error bars represent confidence intervals calculated in Model 3. (B) Difference in total residual variance in Model 5 versus in Model 3. (C) Random effects

estimates from Model 5. (D) Comparison of estimates from Model 6 versus Model 5. Horizontal error bars represent confidence interval calculated in Model 6; vertical error bars represent confidence intervals calculated in Model 5. (E) Difference in Akaike Information Criterion in Model 6 versus in Model 5. (F) Random effects estimates from Model 6.

include additional fixed effects such as sociodemographic variables or recruitment site as covariates. To test whether the inclusion of such variables led to changes in our random effects estimates, we ran several of our original models with additional variables included in the pre-residualization step (i.e., site, parental education, income, and the first ten genetic principal components). Figure 6 shows the results of this model comparison applied to Model 1 (the “classic” ACE model). Supplementary Fig. 3 shows the same

pre-residualization and model comparison applied to Models 2–4 and 6. In the classic ACE model, the *A* estimate tended to decrease and the *C* estimate tended to decrease in the models that included additional covariates (Fig. 6A). Residualizing for additional covariates led to a decrease in the total residual variance across all phenotypes, with decreases ranging from –2.67% (RAVLT) to –26.02% in the ACE model (crystallized cognition; Fig. 6B). Because the two models were run on different datasets (pre-residualized

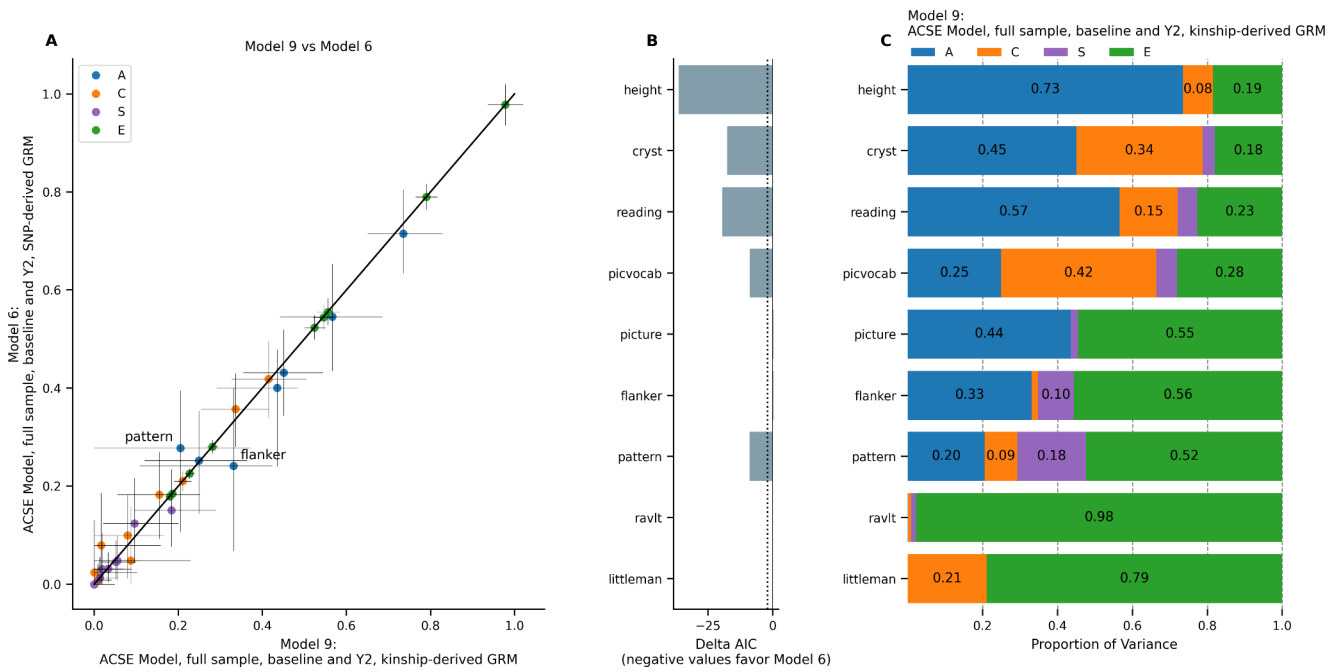


Fig. 5 ACSE model using SNP-derived (Model 6) versus kinship-derived genetic relatedness (Model 9), full sample, baseline + year 2. (A) Comparison of estimates from Model 9 versus Model 6. Horizontal error bars represent confidence interval calculated in Model 9; vertical error bars represent confidence intervals calculated in Model 6. (B) Difference in Akaike Information Criterion in Model 9 versus in Model 6. (C) Random effects estimates from Model 9.

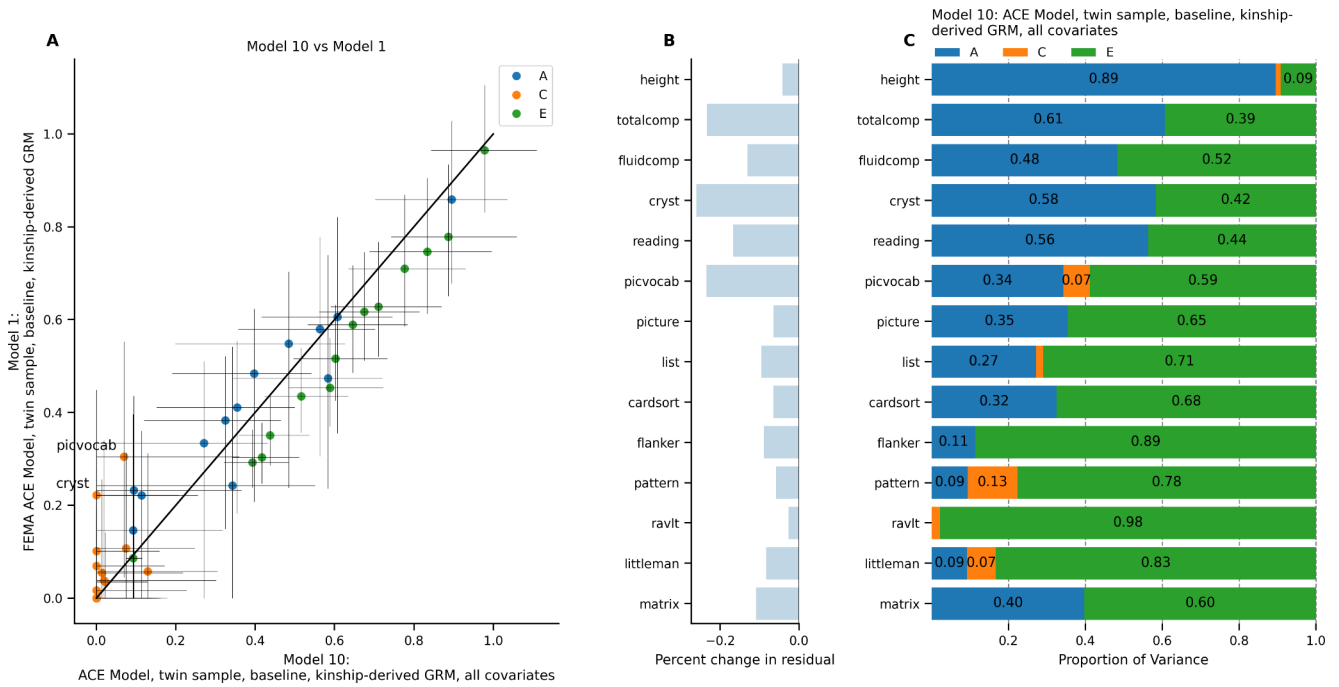


Fig. 6 ACE model in twin sub-sample at baseline, residualizing for all covariates (Model 10) versus age and sex only (Model 1). (A) Comparison of estimates from Model 10 versus Model 1. Horizontal error bars represent confidence interval calculated in Model 10; vertical error bars represent confidence intervals calculated in Model 1. (B) Difference in total residual variance in Model 10 versus in Model 1. (C) Random effects estimates from Model 10.

for different covariates), we did not calculate the difference in AIC between the two models. Figure 6 C and Supplementary Fig. 3C, 3 F, and 3I show the random effects variances for the models that were residualized for additional covariates. In general, the inclusion of additional fixed effects led to lower residual variance being attributed to the random effects of interest, and a lower proportion of the remaining variance was attributed to *A* and *C*.

Effect of Removing the twin-enriched Sample (Models 14–15)

The size and structure of the ABCD Study® cohort, with its embedded twin sub-sample as well as the large number of related participants, led us to test the degree to which the model fit depended on having a large subset of MZ and DZ twins. This question was motivated by the fact that many large cohort studies do not include a specifically twin-enriched sample; we aimed to explore whether such studies can realistically perform similar models to those tested in this paper.

As a proxy for the general population, we removed the twin sub-sample. This left a small number of twins and triplets recruited through the general recruitment pipeline (168 twin pairs and 6 sets of triplets, with 57 pairs of participants with genetic relatedness >0.9 across the full sample). The number of twin and triplet sets in this sample (174 out

of 8131 pregnancies, 2.14%) was less than the 3.11% twin birth rate reported in the general population of the United States (Osterman et al. 2021). We therefore assumed that the ABCD Study® sample excluding the embedded twin sub-sample was a proxy for a population sample with a naturally occurring number of twins. We then fit an ACSE model, applied to the full sample excluding the twin sub-sample, at baseline and year 2, to represent the “best” model possible of those explored thus far, excluding the *T* random effect (Model 15). We compared this model to the same ACSE model applied to the full sample, inclusive of twins (Model 14).

A comparison of the parameter estimates is shown in Fig. 7A. The model excluding the twin sub-sample led to a difference in *A* estimates of -0.19 (picture sequence memory task) to +0.13 (pattern comparison). Excluding the twin sub-sample led to an increase in the total residual variance across all phenotypes, with changes ranging from +0.24% (pattern comparison) to +17.55% (Little Man Task; Fig. 7B). Because the two models were fit to different samples, it was not possible to directly compare model fit from the likelihood statistics. Figure 7 C shows the random effects estimates from the model that omitted the twin sub-sample participants. Overall, excluding the twin sub-sample led to larger total residual variance, with varied effects on heritability estimates.

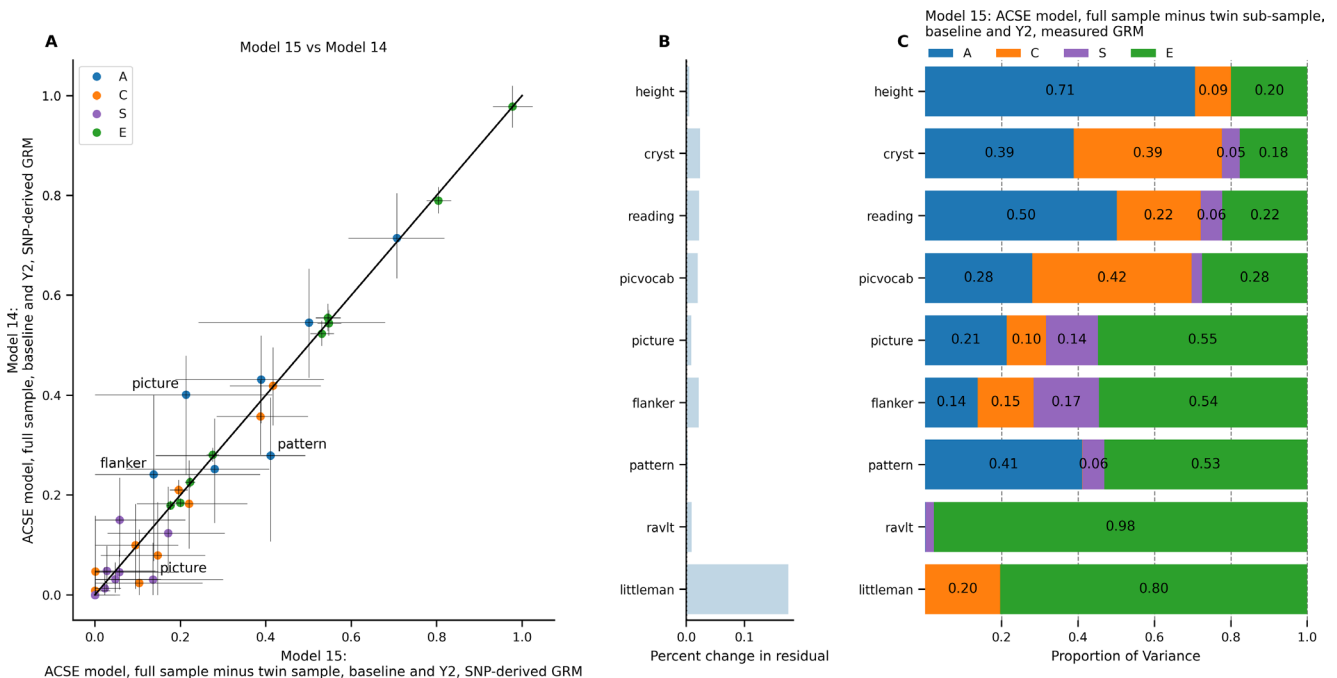


Fig. 7 ACSE model in full sample omitting twin registry participants, baseline + year 2 longitudinal sample (Model 15). Comparison model is equivalent but includes the full sample inclusive of twin registry participants (Model 14). (A) Comparison of estimates from Model 15 versus Model 14. Horizontal error bars represent confidence interval

calculated in Model 15; vertical error bars represent confidence intervals calculated in Model 14. (B) Difference in total residual variance in Model 15 versus in Model 14. (C) Random effects estimates from Model 15.

Discussion

In this paper we present results from different modeling strategies for implementing the ACE model using LMEs, as implemented in FEMA. FEMA is capable of applying the ACE model as well as incorporating additional features such as using a sparse matrix of within-family genetic relatedness and a random effect of subject to model longitudinal data. Notably, the use of FEMA to incorporate relatedness across all subjects within a family allows for the flexibility to include the full ABCD Study[®] sample, rather than restricting analysis to the twin sub-sample. Future updates to the ABCD Study[®] Data Exploration and Analysis Portal will incorporate an online implementation of FEMA so that users can specify mixed effects models of interest using the ABCD Study[®] dataset. In addition, future analyses will incorporate random effects estimates across the high-dimensional brain imaging data present in the ABCD Study[®].

We first applied the ACE model in the baseline twin sample. FEMA and *OpenMx* found nearly equivalent estimates for all random effects variances, demonstrating the equivalence of the two models being fitted. We estimated the heritability of height at 0.86, which is near the top of the range of twin heritability estimates reported by a comparative study of twin cohorts in eight countries (ranging from 0.68 to 0.87; Silventoinen et al. 2003). Our twin heritability estimate for height was higher than the SNP heritability, which was recently estimated to be 40% of phenotypic variance in European ancestry populations and 10–20% in other ancestries (Yengo et al. 2022). Of the cognitive phenotypes, we found the highest twin heritability estimate for total composite cognition (0.61) and oral reading recognition (0.58), consistent with prior findings that heritability estimates tend to be higher for more “crystallized” and culturally sensitive measures of cognition (Kan et al. 2013). Interestingly, the picture vocabulary test had a relatively lower heritability estimate in this model (0.24) compared to the reading recognition test (0.58), which may reflect a difference in the cultural sensitivity of the two “crystallized” cognition tasks. The NIH Toolbox tasks comprising fluid cognition (flanker task, picture sequence memory task, list sorting, pattern comparison, and dimensional card sort) ranged in heritability estimates from 0.22 (flanker) to 0.41 (picture), which is within the wide range of heritability estimates for similar tasks in children (approximately 0–0.6; see Kan et al. 2013). Interestingly, the RAVLT had near-zero estimates for all random effects variances in all models, indicating that this task may be exceptionally unreliable in this sample, or perhaps particularly prone to variance in measurement. For further information regarding the heritability of 14,500 phenotypes in the ABCD Study[®] baseline sample, see recent work by Maes and colleagues (2023).

We next tested the change in model fit and parameter estimation when using SNP-derived genetic relatedness rather than kinship-derived relatedness. Parameter estimates were largely unchanged, reflecting that in a twin sample, the kinship-derived relatedness values of 0.5 and 1 are sufficient to arrive at similar random effects estimates compared to models using SNP-derived relatedness (though the model fit was improved with the SNP-derived relatedness values for several phenotypes). Based on these results, researchers who are deciding between using SNP-derived or kinship-derived relatedness data to model cognitive phenotypes may prefer to choose based on practical considerations (such as availability of different data types, or the relevance of each relatedness estimate to the research question of interest) rather than making a categorical decision based on model fit.

Perhaps one of the most exciting applications comes when extending the model to the full ABCD Study[®] sample. By leveraging the sparse clustering method used by FEMA to handle genetic relatedness only for participants within families, we were able to take advantage of the diverse distribution of genetic relatedness, ranging from 0 (e.g. adopted siblings) to 1 (i.e., MZ twins) for any pair of participants within a family. Unlike the large computational load generated by other similar genome-based REML regressions, the use of sparse clusters allowed FEMA to dramatically cut the computational time (Fan et al. 2021), allowing all the analyses in this paper to be fit on a single machine without the use of parallel computing. Using the full sample, first at baseline then with the addition of the Year 2 data, led to narrower confidence intervals, as shown in Fig. 3. Inclusion of the full sample led to lower heritability estimates for several cognitive phenotypes, which may be related to the relative homogeneity of the twin sub-sample leading to potential for overestimation of heritability. Of note, though singletons (participants who are the sole members of their family cluster) did not contribute to estimation of the random effects variances themselves, they did contribute to the estimation of the total variance, which allows the model to leverage the full ABCD Study[®] sample.

When including the full ABCD Study[®] sample, the total variance in the cognitive phenotypes was larger than the total variance in the twin sub-sample. In the full sample, *C* explained a greater proportion of the total variance than in the twin sub-sample where *C* was small for most phenotypes. This result would indicate that the twin sub-sample may be more homogenous compared to the full study sample with respect to common environment. The twin sub-sample consists of twins recruited via birth registries at the four “Twin Hub” sites (Iacono et al. 2018), whereas the full ABCD Study[®] sample was recruited across twenty one sites, primarily through demographically informed school

selection (for details, see Garavan et al. 2018). A study of over 18 million births spanning 72 countries found twin birth to be associated with maternal health conditions, health behaviors, and socioeconomic characteristics (Bhalotra and Clarke 2016). It is possible that these differences result in the observed differences in total variance and variance components. The underlying causes of this discrepancy, though beyond the scope of this paper, are a worthwhile topic for future research.

After expanding the model to include the full sample, we tested the effect of an added random effect of twin status (i.e., “pregnancy ID”). This T effect could include any components of the environment that are shared between twins but not among siblings. Examples could include shared uterine environment and prenatal factors, such as gestational age; or the fact that twins experience the same environmental events at exactly the same time. To illustrate this point, a pair of twins might experience a global pandemic at exactly the same age, causing them to experience any effects of the event in similar ways. In contrast, if two siblings are different ages at the time of the event, it might have a different age-dependent effect on each of them (despite the fact that it is occurring as part of their “common environment”). Interestingly, although we found evidence for a T effect in matrix reasoning, with a compensatory decrease in the heritability estimate when T was included in the model, the estimated T effect for the other phenotypes of interest was small to none, as shown in Supplementary Fig. 1. One factor that may influence this result is potential overlap between C and T ; in other words, the majority of participants with shared environment are twin pairs, rendering C and T cross-estimable and hard to fit. Future studies, including those without access to a large twin sample, may still benefit from modeling the T effect when there are more similar amounts of twin pairs versus sibling pairs.

We next used the complete sample across multiple timepoints, for a total of over 13,000 observations (Fig. 4). Adding the second timepoint led to a substantial decrease in the heritability estimate for height, with a similar increase in the E component for height. This may be due to several factors, including possible nonadditive genetic effects (e.g., Silventoinen et al. 2008). Conversely, many of the cognitive phenotypes (with the exception of the Little Man Task and the RAVLT) saw an increase in heritability estimates when modeled across multiple timepoints (Fig. 4D). It is possible that this phenomenon is related to the well documented increase in apparent heritability of cognitive traits with age (Davis et al. 2009; Haworth et al. 2010), which may be due in part to the gene \times environment correlation (Loughnan et al. 2019). The S variance component, representing variance that is unexplained by the other random effects, but which remains stable for a given participant, varied by phenotype.

Height had a negligible S component, which may be due to the large amount of variance that was already explained by genetic and environmental effects. On the other hand, the NIH Toolbox tasks each had a variance component explained by subject-level variance, indicating that variance in these phenotypes may be relatively more stable for a given participant over time. For these tasks, including S in our model allows for better explanation of variance that would otherwise be unexplained in a cross-sectional study. The Little Man Task and the RAVLT did not exhibit subject-specific variance, which may be related to higher noise in these measures as evidenced by the large E components for both tasks (0.79 and 0.97 in Model 6, respectively).

Of all the models described in this paper, the model including A , C , S , and E , fit across the full ABCD Study[®] sample and using all timepoints (Model 6), represented the “most complete” model. However, we employed a series of model comparisons to assess the effect of various study design considerations on the random effects variances. First, we examined the change in our model results when using only kinship-derived genetic relatedness, to approximate a study design in which genetic data are not readily available. We found that, as expected, the model fit was worse in this model, but the parameter estimates were generally similar. Of note, we deliberately used the twin sub-sample data to “assign” relatedness values, meaning that for these analyses the twins recruited through the general population were assumed to have a relatedness value of 0.5 regardless of genetic zygosity. Despite this deliberate attempt to increase the error in our model, estimates remained relatively similar, with inflated estimates for the T variance component that seemed to compensate for the induced error in relatedness values (Supplementary Fig. 2). These results indicate that when using kinship-derived relatedness, variance that would have been attributed to increased genetic relatedness is “shifted” into the T component.

We next tested whether including additional covariates in our pre-residualization step would lead to a change in random effects estimates. In general, residualizing for sociodemographic and genetic ancestry covariates led to a decrease in the total residual variance as well as the common environment (C) parameter estimate. This was expected, as adjusting for additional covariates led to a better model fit; the improved model fit was accompanied by a smaller amount of residual variance that was not accounted for by the fixed effects, and any variance that would have been partitioned into C was already attributed to the covariates such as household income or parental education. Notably, adjusting for genetic principal components is an attempt to include potential influences of population stratification in the model, and does not influence the estimation of genetic relatedness. Due to the nesting structure of the random

effects, the FEMA package only uses the pairwise genetic similarity between individuals within the same family. This contrasts with the genetic principal components, which are used to estimate a fixed effect across the whole sample that may represent population stratification and other effects of genetic ancestry.

Finally, we tested whether omitting the twin sub-sample led to a difference in model results. This analysis was based on the fact that many large cohort studies do not contain a twin-enriched sample, and it is unclear whether these datasets can still provide estimates of heritability and other variance components. Overall, heritability estimates only slightly changed for several phenotypes, with two notable exceptions (the picture sequence memory task and pattern comparison processing speed, which decreased by 0.19 and increased by 0.13, respectively). The confidence intervals generated by the two models were similar. Notably, there were over a thousand families containing more than one participant, leading to several hundred families remaining after the removal of the twin sub-sample. The large number of siblings, perhaps in combination with the use of SNP-derived relatedness covering a range of values, as well as the contribution from the twins that remained in this sample, were likely related to the similarity between these results and those obtained from the full ABCD Study[®] sample. Conversely, although large cohort studies such as the ABCD Study[®] are becoming increasingly common, these results also imply that a smaller twin study may be able to achieve similar heritability estimates to those generated through larger cohort studies.

The results from this study should be considered in light of certain limitations. Generally, LMEs are used to partition the variance in a phenotype of interest into components modeled by random effects; however, models are often built with the assumption that the random effects are mutually independent and follow a normal distribution with mean 0 (Neale and Maes 2004; Wang et al. 2011). Additionally, LMEs represent a “top-down” heritability estimation method that can be biased by several factors including gene–environment correlations, selection, non-random mating, and inbreeding (Zaitlen and Kraft 2012; Zhang and Sun 2022). Furthermore, we did not explore non-additive genetic effects, which can attenuate bias of heritability estimates (Wang et al. 2011); nor did we model any gene \times environment interactions, which are likely to exist for some of the phenotypes of interest (Loughnan et al. 2019). Finally, we did not consider sibling interaction in our models, which may interfere with model results due to the potential for different variances in MZ twins compared to DZ twins and full siblings (Eaves 1976).

This work describes many of the modeling techniques available for researchers interested in applying the ACE

model and its extensions to a large sample with high relatedness such as the ABCD Study[®] sample. Notably, the FEMA package provides a tool for mass univariate estimation of LMEs, and its current implementation does not allow for bivariate mixed models. The ability to incorporate multivariate genetic analysis is a major strength of SEM including *OpenMx* (Neale and Maes 2004), and often these techniques are used for more complex models such as factor analysis or interactions among siblings (see Eaves 1976 for an in-depth discussion of sibling interaction). SEM and other implementations of bivariate linear mixed models may therefore provide an avenue to address questions involving genetic and environmental correlations between variables, as well as changes in variance component estimates over time. Bivariate models may also provide some insight into questions of innovation, i.e., whether the set of genes that influence a given phenotype changes over time. In contrast, the mixed effects model used by FEMA leverages the mass univariate approach in a way that allows models to scale to very large datasets spanning multiple timepoints (Fan et al. 2021).

The last several years have seen the development of several new techniques that can be used to model additional relationships, such as random effect \times time interaction (He et al. 2016), random effect \times covariate interaction (Arbet et al. 2020), covariance among random effects (Zhou et al. 2020; Dolan et al. 2021), and allowing random effects estimates to vary as a function of the phenotype (Azzolini et al. 2022). The sparse clustering design employed in the FEMA package leads to improved computational efficiency compared to other LME implementation software (Fan et al. 2021); future work will investigate the use of FEMA to estimate random effects estimates in more high-dimensional datasets, such as the brain imaging data present in the ABCD Study[®], and compare with other computationally efficient implementations of the ACE Model such as Accelerated Permutation Inference for the ACE Model (APACE; Chen et al. 2019) and positive semidefinite ACE (PSD-ACE; Risk and Zhu 2021). More broadly, as stated by Zyphur and colleagues (2013), “top down” heritability estimates should serve as just one piece of the puzzle connecting genes and the environment, where current techniques at the molecular and single-gene level may be useful in filling in the gaps from the bottom up.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10519-023-10141-2>.

Acknowledgements The authors wish to thank the youth and families participating in the ABCD Study[®] and all staff involved in data collection and curation. Dr. Dale reports that he was a Founder of and holds equity in CorTechs Labs, Inc., and serves on its Scientific Advisory Board. He is a member of the Scientific Advisory Board of Human

Longevity, Inc. He receives funding through research grants from GE Healthcare to UCSD. The terms of these arrangements have been reviewed by and approved by UCSD in accordance with its conflict of interest policies. Dr. Andreassen has received speaker's honorarium from Sunovion, Lundbeck and Janssen, and is a consultant for CorTechs.ai.

Authors' Contributions **Conceptualization:** Diana M. Smith, Anders M. Dale; **Methodology:** Diana M. Smith, Robert Loughnan, Naomi P. Friedman, Oleksander Frei, Wesley K. Thompson, Michael Neale, Anders M. Dale; **Formal analysis and investigation:** Diana M. Smith; **Writing - original draft preparation:** Diana M. Smith; **Writing - review and editing:** Robert Loughnan, Naomi P. Friedman, Pravesh Parekh, Wesley K. Thompson, Ole A. Andreassen, Michael Neale, Terry L. Jernigan, Anders M. Dale; **Funding acquisition:** Diana M. Smith, Terry L. Jernigan; **Resources:** Oleksander Frei, Michael Neale, Anders M. Dale; **Supervision:** Wesley K. Thompson, Ole A. Andreassen, Michael Neale, Terry L. Jernigan, Anders M. Dale.

Funding Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive DevelopmentSM Study (ABCD Study[®]; <https://abcdstudy.org>), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children aged 9–10 and follow them over 10 years into early adulthood. The ABCD Study[®] is supported by the National Institutes of Health, USA, and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, U24DA041147, U01DA041093, and U01DA041025. A full list of supporters is available at <https://abcdstudy.org/federal-partners>. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/consortium_members. ABCD Study[®] consortium investigators designed and implemented the study and/or provided data but did not all necessarily participate in analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD Study[®] consortium investigators. The ABCD Study[®] data repository grows and changes over time. The data were downloaded from the NIMH Data Archive ABCD Study[®] Collection Release 4.0 (DOI: <https://doi.org/10.15154/1523041>). This work was supported by Kavli Institute for Brain and Mind Innovative Research Grant 2022–2195.

Data Availability ABCD Study[®] data release 4.0 is available for approved researchers in NIMH Data Archive (NDA; <https://doi.org/10.15154/1523041>).

Code Availability Code for this project is available at <https://github.com/dmysmith/behav-genet-2023>. FEMA is available at https://github.com/cmig-research-group/cmig_tools.

Declarations

Ethics Approval The ABCD Study[®] protocols were approved by the University of California, San Diego Institutional Review Board.

Consent to Participate Parent/caregiver permission and child assent were obtained from each participant.

Consent for Publication Not applicable.

Competing Interests The remaining authors have no conflicts of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

- Acker W (1982) A computerized approach to psychological screening—the Bexley-Maudsley Automated Psychological Screening and the Bexley-Maudsley Category sorting test. *Int J Man-Mach Stud* 17:361–369. [https://doi.org/10.1016/S0020-7373\(82\)80037-0](https://doi.org/10.1016/S0020-7373(82)80037-0)
- Akaike H (1974) A new look at the statistical model identification. *IEEE Trans Autom Control* 19:716–723. <https://doi.org/10.1109/TAC.1974.1100705>
- Akshoomoff N, Beaumont JL, Bauer PJ, Dikmen SS, Gershon RC, Mungas D, Slotkin J, Tulsky D, Weintraub S, Zelazo PD (2013) VIII. NIH Toolbox Cognition Battery (CB): composite scores of crystallized, fluid, and overall cognition. *Monogr Soc Res Child Dev* 78:119–132
- Anokhin AP, Luciana M, Banich M, Barch D, Bjork JM, Gonzalez MR, Gonzalez R, Haist F, Jacobus J, Lisdahl K, McGlade E, McCandliss B, Nagel B, Nixon SJ, Tapert S, Kennedy JT, Thompson W (2022) Age-related changes and longitudinal stability of individual differences in ABCD Neurocognition measures. *Dev Cogn Neurosci* 54:101078. <https://doi.org/10.1016/j.dcn.2022.101078>
- Arbet J, McGue M, Basu S (2020) A robust and unified framework for estimating heritability in twin studies using generalized estimating equations. *Stat Med* 39:3897–3913. <https://doi.org/10.1002/sim.8564>
- Azzolini F, Berentsen GD, Skaug HJ, Hjelmberg JVB, Kaprio JA (2022) The heritability of BMI varies across the range of BMI—a heritability curve analysis in a twin cohort. *Int J Obes* 46:1786–1791. <https://doi.org/10.1038/s41366-022-01172-6>
- Baurley JW, Edlund CK, Pardamean CI, Conti DV, Bergen AW (2016) Smokescreen: a targeted genotyping array for addiction research. *BMC Genomics* 17:145. <https://doi.org/10.1186/s12864-016-2495-7>
- Bhalotra SR, Clarke D (2016) The Twin Instrument. SSRN Electron J. <https://doi.org/10.2139/ssrn.2886776>
- Carey G (2003) *Human Genetics for the Social Sciences*. SAGE Publications, Inc., Thousand Oaks, CA
- Chen X, Formisano E, Blokland GAM, Strike LT, McMahon KL, Zubicaray GI, Thompson PM, Wright MJ, Winkler AM, Ge T, Nichols TE (2019) Accelerated estimation and permutation inference for ACE modeling. *Hum Brain Mapp* 40:3488–3507. <https://doi.org/10.1002/hbm.24611>
- Chen X, Kuja-Halkola R, Rahman I, Arpegård J, Viktorin A, Karlsson R, Hägg S, Svensson P, Pedersen NL, Magnusson PKE (2015) Dominant genetic variation and missing heritability for human complex traits: insights from twin versus genome-wide common SNP models. *Am J Hum Genet* 97:708–714. <https://doi.org/10.1016/j.ajhg.2015.10.004>
- Conomos MP, Miller MB, Thornton TA (2015) Robust inference of population structure for ancestry prediction and correction of

- stratification in the presence of relatedness. *Genet Epidemiol* 39:276–293
- Conomos MP, Reiner AP, Weir BS, Thornton TA (2016) Model-free estimation of recent genetic relatedness. *Am J Hum Genet* 98:127–148
- Davis OSP, Haworth CMA, Plomin R (2009) Dramatic increase in heritability of cognitive development from early to middle childhood: an 8-year longitudinal study of 8,700 pairs of twins. *Psychol Sci* 20:1301–1308. <https://doi.org/10.1111/j.1467-9280.2009.02433.x>
- Dolan CV, Huijskens RCA, Minică CC, Neale MC, Boomsma DI (2021) Incorporating polygenic risk scores in the ACE twin model to estimate A–C covariance. *Behav Genet* 51:237–249. <https://doi.org/10.1007/s10519-020-10035-7>
- Eaves L (1976) A model for sibling effects in man. *Heredity* 36:205–214. <https://doi.org/10.1038/hdy.1976.25>
- Eaves LJ, Pourcain BSt, Smith GD, York TP, Evans DM (2014) Resolving the effects of maternal and offspring genotype on dyadic outcomes in genome wide complex trait analysis (“M-GCTA”). *Behav Genet* 44:445–455. <https://doi.org/10.1007/s10519-014-9666-6>
- Eilertsen EM, Jami ES, McAdams TA, Hannigan LJ, Havdahl AS, Magnus P, Evans DM, Ystrom E (2021) Direct and indirect effects of maternal, paternal, and offspring genotypes: Trio-GCTA. *Behav Genet* 51:154–161. <https://doi.org/10.1007/s10519-020-10036-6>
- Fan CC, McGrath JJ, Appadurai V, Buil A, Gandal MJ, Schork AJ, Mortensen PB, Agerbo E, Geschwind SA, Geschwind D, Werge T, Thompson WK, Pedersen CB (2018) Spatial fine-mapping for gene-by-environment effects identifies risk hot spots for schizophrenia. *Nat Commun* 9:5296. <https://doi.org/10.1038/s41467-018-07708-7>
- Fan CC, Palmer CE, Iversen JR, Pecheva D, Holland D, Frei O, Thompson WK, Hagler DJ, Andreassen OA, Jernigan TL, Nichols TE, Dale AM (2021) FEMA: Fast and efficient mixed-effects algorithm for population-scale whole-brain imaging data. *bioRxiv*. <https://doi.org/10.1101/2021.10.27.466202>
- Garavan H, Bartsch H, Conway K, Decastro A, Goldstein RZ, Heeringa S, Jernigan T, Potter A, Thompson W, Zahs D (2018) Recruiting the ABCD sample: design considerations and procedures. *Dev Cogn Neurosci* 32:16–22. <https://doi.org/10.1016/j.dcn.2018.04.004>
- Ge T, Nichols TE, Lee PH, Holmes AJ, Roffman JL, Buckner RL, Sabuncu MR, Smoller JW (2015) Massively expedited genome-wide heritability analysis (MEGHA). *Proc Natl Acad Sci* 112:2479–2484. <https://doi.org/10.1073/pnas.1415603112>
- Gershon RC, Wagster MV, Hendrie HC, Fox NA, Cook KF, Nowinski CJ (2013) NIH toolbox for assessment of neurological and behavioral function. *Neurology* 80:S2–S6. <https://doi.org/10.1212/WNL.0b013e3182872e5f>
- Gogarten SM, Sofer T, Chen H, Yu C, Brody JA, Thornton TA, Rice KM, Conomos MP (2019) Genetic association testing using the GENESIS R/Bioconductor package. *Bioinformatics* 35:5346–5348
- Haworth CMA, Wright MJ, Luciano M, Martin NG, de Geus EJC, van Beijsterveldt CEM, Bartels M, Posthuma D, Boomsma DI, Davis OSP, Kovas Y, Corley RP, DeFries JC, Hewitt JK, Olson RK, Rhea S-A, Wadsworth SJ, Iacono WG, McGue M, Thompson LA, Hart SA, Petrill SA, Lubinski D, Plomin R (2010) The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Mol Psychiatry* 15:1112–1120. <https://doi.org/10.1038/mp.2009.55>
- He L, Sillanpää MJ, Silventoinen K, Kaprio J, Pitkäniemi J (2016) Estimating modifying effect of age on genetic and environmental variance components in twin models. *Genetics* 202:1313–1328. <https://doi.org/10.1534/genetics.115.183905>
- Heaton RK, Akshoomoff N, Tulskey D, Mungas D, Weintraub S, Dickmen S, Beaumont J, Casaletto KB, Conway K, Slotkin J, Gershon R (2014) Reliability and validity of Composite Scores from the NIH Toolbox Cognition Battery in adults. *J Int Neuropsychol Soc* 20:588–598. <https://doi.org/10.1017/S1355617714000241>
- Heckerman D, Gurdasani D, Kadie C, Pomilla C, Carstensen T, Martin H, Ekoru K, Nsubuga RN, Ssenyomo G, Kamali A, Kaleebu P, Widmer C, Sandhu MS (2016) Linear mixed model for heritability estimation that explicitly addresses environmental variation. *Proc Natl Acad Sci* 113:7377–7382. <https://doi.org/10.1073/pnas.1510497113>
- Iacono WG, Heath AC, Hewitt JK, Neale MC, Banich MT, Luciano MM, Madden PA, Barch DM, Bjork JM (2018) The utility of twins in developmental cognitive neuroscience research: how twins strengthen the ABCD research design. *Dev Cogn Neurosci* 32:30–42. <https://doi.org/10.1016/j.dcn.2017.09.001>
- Kan K-J, Wicherts JM, Dolan CV, van der Maas HLJ (2013) On the nature and nurture of intelligence and specific cognitive abilities: the more heritable, the more culture dependent. *Psychol Sci* 24:2420–2428. <https://doi.org/10.1177/0956797613493292>
- Keller MC, Medland SE, Duncan LE, Hatemi PK, Neale MC, Maes HHM, Eaves LJ (2009) Modeling extended twin family data I: description of the cascade model. *Twin Res Hum Genet* 12:8–18. <https://doi.org/10.1375/twin.12.1.8>
- Kim Y, Lee Y, Lee S, Kim NH, Lim J, Kim YJ, Oh JH, Min H, Lee M, Seo H-J, Lee S-H, Sung J, Cho NH, Kim B-J, Han B-G, Elston RC, Won S, Lee J (2015) On the estimation of heritability with family-based and population-based samples. *BioMed Res Int* 2015:1–9. <https://doi.org/10.1155/2015/671349>
- Kirkpatrick RM, Pritikin JN, Hunter MD, Neale MC (2021) Combining structural-equation modeling with genomic-relatedness-matrix restricted maximum likelihood in OpenMx. *Behav Genet* 51:331–342. <https://doi.org/10.1007/s10519-020-10037-5>
- Loughnan RJ, Palmer CE, Thompson WK, Dale AM, Jernigan TL, Fan CC (2019) Gene-experience correlation during cognitive development: evidence from the adolescent brain Cognitive Development (ABCD) study. <https://doi.org/10.1101/637512>. *bioRxiv*
- Maes HHM, Lapato DM, Schmitt JE, Luciana M, Banich MT, Bjork JM, Hewitt JK, Madden PA, Heath AC, Barch DM, Thompson WK, Iacono WG, Neale MC (2023) Genetic and environmental variation in continuous phenotypes in the ABCD Study®. *Behav Genet* 53:1–24. <https://doi.org/10.1007/s10519-022-10123-w>
- Martin NG, Eaves LJ (1977) The genetical analysis of covariance structure. *Heredity* 38:79–95. <https://doi.org/10.1038/hdy.1977.9>
- McArdle JJ, Prescott CA (2005) Mixed-effects variance components models for biometric family analyses. *Behav Genet* 35:631–652. <https://doi.org/10.1007/s10519-005-2868-1>
- Neale MC, Hunter MD, Pritikin JN, Zahery M, Brick TR, Kirkpatrick RM, Estabrook R, Bates TC, Maes HH, Boker SM (2016) OpenMx 2.0: extended structural equation and statistical modeling. *Psychometrika* 81:535–549. <https://doi.org/10.1007/s11336-014-9435-8>
- Neale MC, Maes HHM (2004) Methodology for genetic studies of twins and families. Kluwer Academic Publishers B.V., Dordrecht, NL
- Neale MC, Miller MB (1997) The use of likelihood-based confidence intervals in genetic models. *Behav Genet* 27:113–120. <https://doi.org/10.1023/A:1025681223921>
- Osterman M, Hamilton B, Martin J, Driscoll A, Valenzuela C (2021) Births: final data for 2020. National Center for Health Statistics (U.S).
- Pinheiro JC (2014) Linear mixed effects models for longitudinal data. In: Balakrishnan N, Colton T, Everitt B, Piegorisch W, Ruggeri F, Teugels JL (eds) Wiley StatsRef: Statistics Reference Online, 1st edn. Wiley

- Qiao Z, Zheng J, Helgeland Ø, Vaudel M, Johansson S, Njølstad PR, Smith GD, Warrington NM, Evans DM (2020) Introducing M-GCTA a software package to estimate maternal (or paternal) genetic effects on offspring phenotypes. *Behav Genet* 50:51–66. <https://doi.org/10.1007/s10519-019-09969-4>
- Rabe-Hesketh S, Skrondal A, Gjessing HK (2008) Biometrical modeling of twin and family data using standard mixed model software. *Biometrics* 64:280–288. <https://doi.org/10.1111/j.1541-0420.2007.00803.x>
- Risk BB, Zhu H (2021) ACE of space: estimating genetic components of high-dimensional imaging data. *Biostatistics* 22:131–147. <https://doi.org/10.1093/biostatistics/kxz022>
- Schmidt M (1996) *Rey auditory verbal learning test: a handbook*. Western Psychological Services, Los Angeles, CA
- Silventoinen K, Pietiläinen KH, Tynelius P, Sørensen TIA, Kaprio J, Rasmussen F (2008) Genetic regulation of growth from birth to 18 years of age: the swedish young male twins study. *Am J Hum Biol* 20:292–298. <https://doi.org/10.1002/ajhb.20717>
- Silventoinen K, Sarmalisto S, Perola M, Boomsma DI, Cornes BK, Davis C, Dunkel L, de Lange M, Harris JR, Hjelmborg JVB, Luciano M, Martin NG, Mortensen J, Nisticò L, Pedersen NL, Skytthe A, Spector TD, Stazi MA, Willemsen G, Kaprio J (2003) Heritability of adult body height: a comparative study of twin cohorts in eight countries. *Twin Res* 6:399–408. <https://doi.org/10.1375/136905203770326402>
- Sprott DA (2000) *Statistical inference in science*. Springer, New York
- Truett KR, Eaves LJ, Walters EE, Heath AC, Hewitt JK, Meyer JM, Silberg J, Neale MC, Martin NG, Kendler KS (1994) A model system for analysis of family resemblance in extended kinships of twins. *Behav Genet* 24:35–49. <https://doi.org/10.1007/BF01067927>
- Urban KA, Horton MK, Jacobus J, Heyser C, Thompson WK, Tapert SF, Madden PAF, Sowell ER (2018) Biospecimens and the ABCD study: Rationale, methods of collection, measurement and early data. *Dev Cogn Neurosci* 32:97–106. <https://doi.org/10.1016/j.dcn.2018.03.005>
- Visscher PM, Benyamin B, White I (2004) The use of linear mixed models to estimate variance components from data on twin pairs by maximum likelihood. *Twin Res Hum Genet* 7:670–674. <https://doi.org/10.1375/twin.7.6.670>
- Volkow ND, Koob GF, Croyle RT, Bianchi DW, Gordon JA, Koroshetz WJ, Pérez-Stable EJ, Riley WT, Bloch MH, Conway K, Deeds BG, Dowling GJ, Grant S, Howlett KD, Matochik JA, Morgan GD, Murray MM, Noronha A, Spong CY, Wargo EM, Warren KR, Weiss SRB (2018) The conception of the ABCD study: from substance use to a broad NIH collaboration. *Dev Cogn Neurosci* 32:4–7. <https://doi.org/10.1016/j.dcn.2017.10.002>
- Wainschtein P, Jain D, Zheng Z, TOPMed Anthropometry Working Group, Aslibekyan S, Becker D, Bi W, Brody J, Carlson JC, Correa A, Du MM, Fernandez-Rhodes L, Ferrier KR, Graff M, Guo X, He J, Heard-Costa NL, Highland HM, Hirschhorn JN, Howard-Claudio CM, Isasi CR, Jackson R, Jiang J, Joehanes R, Justice AE, Kalyani RR, Kardia S, Lange E, LeBoff M, Lee S, Li X, Li Z, Lim E, Lin D, Lin X, Liu S, Lu Y, Manson J, Martin L, McHugh C, Mikulla J, Musani SK, Ng M, Nickerson D, Palmer N, Perry J, Peters U, Preuss M, Qi Q, Raffield L, Rasmussen-Torvik L, Reiner A, Russell EM, Sitlani C, Smith J, Spracklen CN, Wang T, Wang Z, Wessel J, Xu H, Yaser M, Yoneyama S, Young KA, Zhang J, Zhang X, Zhou H, Zhu X, Zoellner S, NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium, Abe N, Abecasis G, Aguet F, Almasy L, Alonso A, Ament S, Anderson P, Anugu P, Applebaum-Bowden B, Ardlie K, Arking D, Ashley-Koch A, Assimes T, Auer P, Avramopoulos D, Ayas N, Balasubramanian A, Barnard J, Barnes K, Barr RG, Barron-Casella E, Barwick L, Beaty T, Beck G, Becker L, Beer R, Beitelshes A, Benjamin E, Benos T, Bezerra M, Bielak L, Bis J, Blackwell T, Blangero J, Bowden DW, Bowler R, Broeckel U, Broome J, Brown D, Bunting K, Burchard E, Bustamante C, Buth E, Cade B, Cardwell J, Carey V, Carrier J, Carson A, Carty C, Casaburi R, Romero JPC, Casella J, Castaldi P, Chaffin M, Chang C, Chang Y-C, Chavan S, Chen B-J, Chen W-M, Cho M, Choi SH, Chuang L-M, Chung R-H, Clish C, Comhair S, Conomos M, Cornell E, Crandall C, Crapo J, Curran J, Curtis J, Custer B, Damcott C, Darbar D, David S, Davis C, Daya M, de las Fuentes L, de Vries P, DeBaun M, Dekker R, DeMeo D, Devine S, Dinh H, Doddapaneni H, Duan Q, Dugan-Perez S, Duggirala R, Durda JP, Dutcher SK, Eaton C, Ekunwe L, El Bouciz A, Emery L, Erzurum S, Farber C, Farek J, Fingerlin T, Flickinger M, Franceschini N, Frazier C, Fu M, Fullerton SM, Fulton L, Gabriel S, Gan W, Gao S, Gao Y, Gass M, Geiger H, Gelb B, Geraci M, Germer S, Gerszten R, Ghosh A, Gibbs R, Gignoux C, Gladwin M, Glahn D, Gogarten S, Gong D-W, Goring H, Graw S, Gray KJ, Grine D, Gross C, Gu CC, Guan Y, Gupta N, Haas DM, Haessler J, Hall M, Han Y, Hanly P, Harris D, Hawley NL, Heavner B, Herrington D, Hersh C, Hidalgo B, Hixson J, Hobbs B, Hokanson J, Hong E, Hoth K, Hsiung CA, Hu J, Hung Y-J, Huston H, Hwu CM, Irvin MR, Jaquish C, Johnson J, Johnson A, Johnson C, Johnston R, Jones K, Kang HM, Kaplan R, Kelly S, Kenny E, Kessler M, Khan A, Khan Z, Kim W, Kimoff J, Kinney G, Konkole B, Kramer H, Lange C, Lee J, Lee S, Lee W-J, LeFaive J, Levine D, Levy D, Lewis J, Li X, Li Y, Lin H, Lin H, Liu Y, Liu Y, Lunetta K, Luo J, Magalang U, Mahaney M, Make B, Manichaikul A, Manning A, Marton M, Mathai S, May S, McArdle P, McFarland S, McGoldrick D, McNeil B, Mei H, Meigs J, Menon V, Mestroni L, Metcalf G, Meyers DA, Mignot E, Mikulla J, Min N, Minear M, Minster RL, Moll M, Momin Z, Montasser ME, Montgomery C, Muzny D, Mychaleckyj JC, Nadkarni G, Naik R, Naseri T, Natarajan P, Nekhai S, Nelson SC, Neltner B, Nessner C, Nkechinyere O, O'Connor T, Ochs-Balcom H, Okwuonu G, Pack A, Paik DT, Palmer N, Pankow J, Papanicolaou G, Parker C, Peloso G, Peralta JM, Perez M, Peyser P, Phillips LS, Pleiness J, Pollin T, Post W, Becker JP, Boorgula MP, Qasba P, Qiao D, Qin Z, Rafaels N, Rajendran M, Rao DC, Ratan A, Reed R, Reeves C, Reupena MS, Rice K, Robillard R, Robine N, Roselli C, Ruczinski I, Runnels A, Russell P, Ruuska S, Ryan K, Sabino EC, Saleheen D, Salimi S, Salvi S, Salzberg S, Sandow K, Sankaran VG, Santibanez J, Schwander K, Schwartz D, Sciruba F, Seidman C, Seidman J, Sheehan V, Sherman SL, Shetty A, Shetty A, Sheu WH-H, Silver B, Silverman E, Skomro R, Smith AV, Smith J, Smith T, Smoller S, Snively B, Snyder M, Sofer T, Sotoodehnia N, Stilp AM, Storm G, Streeten E, Su JL, Sung YJ, Sylvia J, Szpiro A, Taliun D, Tang H, Taub M, Taylor KD, Taylor M, Taylor S, Telen M, Thornton TA, Threlkeld M, Tinker L, Tirschwell D, Tishkoff S, Tiwari H, Tong C, Tracy R, Tsai M, Vaidya D, Van Den Berg D, VandeHaar P, Vrieze S, Walker T, Wallace R, Walts A, Wang FF, Wang H, Wang J, Watson K, Watt J, Weeks DE, Weinstock J, Weiss ST, Weng L-C, Willer C, Williams K, Williams LK, Wilson C, Wilson J, Winterkorn L, Wong Q, Wu J, Xu H, Yang I, Yu K, Zekavat SM, Zhang Y, Zhao SX, Zhao W, Zody M, Cupples LA, Shadyab AH, McKnight B, Shoemaker BM, Mitchell BD, Psaty BM, Kooperberg C, Liu C-T, Albert CM, Roden D, Chasman DI, Darbar D, Lloyd-Jones DM, Arnett DK, Regan EA, Boerwinkle E, Rotter JI, O'Connell JR, Yanek LR, de Andrade M, Allison MA, McDonald M-LN, Chung MK, Fornage M, Chami N, Smith NL, Ellinor PT, Vasani RS, Mathias RA, Loos RJF, Rich SS, Lubitz SA, Heckbert SR, Redline S, Guo X, Chen Y-DI, Laurie CA, Hernandez RD, McGarvey ST, Goddard ME, Laurie CC, North KE, Lange LA, Weir BS, Yengo L, Yang J, Visscher PM (2022) Assessing the contribution of rare variants to complex trait heritability from whole-genome sequence data. *Nat Genet* 54:263–273. <https://doi.org/10.1038/s41588-021-00997-7>

- Wang X, Guo X, He M, Zhang H (2011) Statistical inference in mixed models and analysis of twin and family data. *Biometrics* 67:987–995. <https://doi.org/10.1111/j.1541-0420.2010.01548.x>
- Wechsler D (2014) WISC-V: Technical and interpretive manual. NCS Pearson, Incorporated
- Wojcik GL, Graff M, Nishimura KK, Tao R, Haessler J, Gignoux CR, Highland HM, Patel YM, Sorokin EP, Avery CL (2019) Genetic analyses of diverse populations improves discovery for complex traits. *Nature* 570:514–518
- Yang J, Lee SH, Goddard ME, Visscher PM (2011) GCTA: a tool for genome-wide Complex Trait Analysis. *Am J Hum Genet* 88:76–82. <https://doi.org/10.1016/j.ajhg.2010.11.011>
- Yengo L, Vedantam S, Marouli E, Sidorenko J, Bartell E, Sakaue S, Graff M, Eliassen AU, Jiang Y, Raghavan S, Miao J, Arias JD, Graham SE, Mukamel RE, Spracklen CN, Yin X, Chen S-H, Ferreira T, Highland HH, Ji Y, Karaderi T, Lin K, Lüll K, Malden DE, Medina-Gomez C, Machado M, Moore A, Rueger S, Sim X, Vrieze S, Ahluwalia TS, Akiyama M, Allison MA, Alvarez M, Andersen MK, Ani A, Appadurai V, Arbeeve L, Bhaskar S, Bielak LF, Bollepalli S, Bonnycastle LL, Bork-Jensen J, Bradfield JP, Bradford Y, Braund PS, Brody JA, Burgdorf KS, Cade BE, Cai H, Cai Q, Campbell A, Cañadas-Garre M, Catamo E, Chai J-F, Chai X, Chang L-C, Chang Y-C, Chen C-H, Chesi A, Choi SH, Chung R-H, Cocca M, Concas MP, Couture C, Cuellar-Partida G, Danning R, Daw EW, Degenhard F, Delgado GE, Delitala A, Demirkan A, Deng X, Devineni P, Dietl A, Dimitriou M, Dimitrov L, Dorajoo R, Ekici AB, Engmann JE, Fairhurst-Hunter Z, Farmaki A-E, Faul JD, Fernandez-Lopez J-C, Forer L, Francescatti M, Freitag-Wolf S, Fuchsberger C, Galesloot TE, Gao Y, Gao Z, Geller F, Giannakopoulou O, Giulianini F, Gjesing AP, Goel A, Gordon SD, Gorski M, Grove J, Guo X, Gustafsson S, Haessler J, Hansen TF, Havulinna AS, Haworth SJ, He J, Heard-Costa N, Hebbar P, Hindy G, Ho Y-LA, Hofer E, Holliday E, Horn K, Hornsby WE, Hottenga J-J, Huang H, Huang J, Huerta-Chagoya A, Huffman JE, Hung Y-J, Huo S, Hwang MY, Iha H, Ikeda DD, Isono M, Jackson AU, Jäger S, Jansen IE, Johansson I, Jonas JB, Jonsson A, Jørgensen T, Kalafati I-P, Kanai M, Kanoni S, Kärhus LL, Kasturiratne A, Katsuya T, Kawaguchi T, Kember RL, Kentistou KA, Kim H-N, Kim Y-J, Kleber ME, Knol MJ, Kurbasic A, Lauzon M, Le P, Lea R, Lee J-Y, Leonard HL, Li SA, Li X, Li X, Liang J, Lin H, Lin S-Y, Liu J, Liu X, Lo KS, Long J, Lores-Motta L, Luan J, Lyssenko V, Lyytikäinen L-P, Mahajan A, Mamakou V, Mangino M, Manichaikul A, Marten J, Mattheisen M, Mavarani L, McDaid AF, Meidtner K, Melendez TL, Mercader JM, Milanecchi Y, Miller JE, Millwood IY, Mishra PP, Mitchell RE, Møllehave LT, Morgan A, Mucha S, Munz M, Nakatochi M, Nelson CP, Nethander M, Nho CW, Nielsen AA, Nolte IM, Nongmaithem SS, Noordam R, Ntalla I, Nutile T, Pandit A, Christofidou P, Pärna K, Pauper M, Petersen ERB, Petersen LV, Pitkänen N, Polašek O, Poveda A, Preuss MH, Pyarajan S, Raffield LM, Rakugi H, Ramirez J, Rasheed A, Raven D, Rayner NW, Riveros C, Rohde R, Ruggiero D, Ruotsalainen SE, Ryan KA, Sabater-Lleal M, Saxena R, Scholz M, Sendamarai A, Shen B, Shi J, Shin JH, Sidore C, Sitlani CM, Sliker RC, Smit RAJ, Smith AV, Smith JA, Smyth LJ, Southam L, Steinthorsdottir V, Sun L, Takeuchi F, Tallapragada DSP, Taylor KD, Tayo BO, Tcheandjieu C, Terzikhan N, Tesolin P, Teumer A, Theusch E, Thompson DJ, Thorleifsson G, Timmers PRHJ, Trompet S, Turman C, Vaccargiu S, van der Laan SW, van der Most PJ, van Klinken JB, van Setten J, Verma SS, Verweij N, Vaturi Y, Wang CA, Wang C, Wang L, Wang Z, Warren HR, Bin Wei W, Wickremasinghe AR, Wielscher M, Wiggins KL, Winsvold BS, Wong A, Wu Y, Wuttke M, Xia R, Xie T, Yamamoto K, Yang J, Yao J, Young H, Youssri NA, Yu L, Zeng L, Zhang W, Zhang X, Zhao J-H, Zhao W, Zhou W, Zimmermann ME, Zoledziewska M, Adair LS, Adams HHH, Aguilar-Salinas CA, Al-Mulla F, Arnett DK, Asselbergs FW, Äsvold BO, Attia J, Banas B, Bandinelli S, Bennett DA, Bergler T, Bharadwaj D, Biino G, Bisgaard H, Boerwinkle E, Böger CA, Bønnelykke K, Boomsma DI, Børghlum AD, Borja JB, Bouchard C, Bowden DW, Brandslund I, Brumpton B, Buring JE, Caulfield MJ, Chambers JC, Chandak GR, Chanock SJ, Chaturvedi N, Chen Y-DI, Chen Z, Cheng C-Y, Christophersen IE, Ciullo M, Cole JW, Collins FS, Cooper RS, Cruz M, Cucca F, Cupples LA, Cutler MJ, Damrauer SM, Dantoft TM, de Borst GJ, de Groot LCPGM, De Jager PL, de Kleijn DPV, Janaka de Silva H, Dedoussis GV, den Hollander AI, Du S, Easton DF, Elders PJM, Eliassen AH, Ellinor PT, Elmstahl S, Erdmann J, Evans MK, Fatkin D, Feenstra B, Feitosa MF, Ferrucci L, Ford I, Fornage M, Franke A, Franks PW, Freedman BI, Gasparini P, Gieger C, Girotto G, Goddard ME, Golightly YM, Gonzalez-Villalpando C, Gordon-Larsen P, Grallert H, Grant SFA, Grarup N, Griffiths L, Gudnason V, Haiman C, Hakonarson H, Hansen T, Hartman CA, Hattersley AT, Hayward C, Heckbert SR, Heng C-K, Hengstenberg C, Hewitt AW, Hishigaki H, Hoynig CB, Huang PL, Huang W, Hunt SC, Hveem K, Hyppönen E, Iacono WG, Ichihara S, Ikram MA, Isasi CR, Jackson RD, Jarvelin M-R, Jin Z-B, Jöckel K-H, Joshi PK, Jousilahti P, Jukema JW, Kähönen M, Kamatani Y, Kang KD, Kaprio J, Kardina SLR, Karpe F, Kato N, Kee F, Kessler T, Khera AV, Khor CC, Kiemeny LALM, Kim B-J, Kim EK, Kim H-L, Kirchhof P, Kivimaki M, Koh W-P, Koistinen HA, Kolovou GD, Kooner JS, Kooperberg C, Köttgen A, Kovacs P, Kraaijeveld A, Kraft P, Krauss RM, Kumari M, Kutalik Z, Laakso M, Lange LA, Langenberg C, Launer LJ, Le Marchand L, Lee H, Lee NR, Lehtimäki T, Li H, Li L, Lieb W, Lin X, Lind L, Linneberg A, Liu C-T, Liu J, Loeffler M, London B, Lubitz SA, Lye SJ, Mackey DA, Mägi R, Magnusson PKE, Marcus GM, Vidal PM, Martin NG, März W, Matsuda F, McGarrah RW, McGue M, McKnight AJ, Medland SE, Mellström D, Metspalu A, Mitchell BD, Mitchell P, Mook-Kanamori DO, Morris AD, Mucci LA, Munroe PB, Nalls MA, Nazarian S, Nelson AE, Neville MJ, Newton-Cheh C, Nielsen CS, Nöthen MM, Ohlsson C, Oldehinkel AJ, Orozco L, Pahkala K, Pajukanta P, Palmer CNA, Parra EJ, Pattaro C, Pedersen O, Pennell CE, Penninx BWJH, Perusse L, Peters A, Peyser PA, Porteous DJ, Posthuma D, Power C, Pramstaller PP, Province MA, Qi Q, Qu J, Rader DJ, Raitakari OT, Rallhan S, Rallidis LS, Rao DC, Redline S, Reilly DF, Reiner AP, Rhee SY, Ridker PM, Rienstra M, Ripatti S, Ritchie MD, Roden DM, Rosendaal FR, Rotter JJ, Rudan I, Rutter F, Sabanayagam C, Saleheen D, Salomaa V, Samani NJ, Sanghera DK, Sattar N, Schmidt H, Schmidt H, Schmidt R, Schulze MB, Schunkert H, Scott LJ, Scott RJ, Sever P, Shiroma EJ, Shoemaker MB, Shu X-O, Simonsick EM, Sims M, Singh JR, Singleton AB, Sinner MF, Smith JG, Snieder H, Spector TD, Stampfer MJ, Stark KJ, Strachan DP, 't Hart LM, Tabara Y, Tang H, Tardif J-C, Thanaraj TA, Timpson NJ, Tönjes A, Tremblay A, Tuomi T, Tuomilehto J, Tusié-Luna M-T, Uitterlinden AG, van Dam RM, van der Harst P, Van der Velde N, van Duijn CM, van Schoor NM, Vitart V, Völker U, Vollenweider P, Völzke H, Wachter-Rodarte NH, Walker M, Wang YX, Wareham NJ, Watanabe RM, Watkins H, Weir DR, Werge TM, Widen E, Wilkens LR, Willemsen G, Willett WC, Wilson JF, Wong T-Y, Woo J-T, Wright AF, Wu J-Y, Xu H, Yajnik CS, Yokota M, Yuan J-M, Zeggini E, Zemel BS, Zheng W, Zhu X, Zmuda JM, Zonderman AB, Zwart J-A, 23andMe Research Team, Partida GC, VA Million Veteran Program, Sun Y, DiscovEHR (DiscovEHR and MyCode Community Health Initiative), eMERGE (Electronic Medical Records and Genomics Network), Croteau-Chonka D, Lifelines Cohort Study, Vonk JM, The PRACTICAL Consortium, Chanock S, Le Marchand L, Understanding Society Scientific Group, Chasman DI, Cho YS, Heid IM, McCarthy MI, Ng MCY, O'Donnell CJ, Rivadeneira F, Thorsteinsdottir U, Sun YV, Tai ES, Boehnke M, Deloukas P, Justice AE, Lindgren CM, Loos RJF, Mohlke KL, North KE,

- Stefansson K, Walters RG, Winkler TW, Young KL, Loh P-R, Yang J, Esko T, Assimes TL, Auton A, Abecasis GR, Willer CJ, Locke AE, Berndt SI, Lettre G, Frayling TM, Okada Y, Wood AR, Visscher PM, Hirschhorn JN (2022) A saturated map of common genetic variants associated with human height. *Nature*. <https://doi.org/10.1038/s41586-022-05275-y>
- Zaitlen N, Kraft P (2012) Heritability in the genome-wide association era. *Hum Genet* 131:1655–1664. <https://doi.org/10.1007/s00439-012-1199-6>
- Zhang L, Sun L (2022) Linear mixed-effect models through the lens of Hardy–Weinberg disequilibrium. *Front Genet* 13:856872. <https://doi.org/10.3389/fgene.2022.856872>
- Zhou X, Im HK, Lee SH (2020) CORE GREML for estimating covariance between random effects in linear mixed models for complex trait analyses. *Nat Commun* 11:4208. <https://doi.org/10.1038/s41467-020-18085-5>
- Zyphur MJ, Zhang Z, Barsky AP, Li W-D (2013) An ACE in the hole: twin family models for applied behavioral genetics research. *Leadersh Q* 24:572–594. <https://doi.org/10.1016/j.leaqua.2013.04.001>

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.