

Archival Report

Genome-wide Analyses of Vocabulary Size in Infancy and Toddlerhood: Associations With Attention-Deficit/Hyperactivity Disorder, Literacy, and Cognition-Related Traits

Ellen Verhoef, Andrea G. Allegrini, Philip R. Jansen, Katherine Lange, Carol A. Wang, Angela T. Morgan, Tarunveer S. Ahluwalia, Christos Symeonides, EAGLE Working Group, Else Eising, Marie-Christine Franken, Elina Hypponen, Toby Mansell, Mitchell Ollislagers, Emina Omerovic, Kaili Rimfeld, Fenja Schlag, Saskia Selzam, Chin Yang Shapland, Henning Tiemeier, Andrew J.O. Whitehouse, Richard Saffery, Klaus Bønnelykke, Sheena Reilly, Craig E. Pennell, Melissa Wake, Charlotte A.M. Cecil, Robert Plomin, Simon E. Fisher, and Beate St. Pourcain

ABSTRACT

BACKGROUND: The number of words children produce (expressive vocabulary) and understand (receptive vocabulary) changes rapidly during early development, partially due to genetic factors. Here, we performed a meta-genome-wide association study of vocabulary acquisition and investigated polygenic overlap with literacy, cognition, developmental phenotypes, and neurodevelopmental conditions, including attention-deficit/hyperactivity disorder (ADHD).

METHODS: We studied 37,913 parent-reported vocabulary size measures (English, Dutch, Danish) for 17,298 children of European descent. Meta-analyses were performed for early-phase expressive (infancy, 15–18 months), late-phase expressive (toddlerhood, 24–38 months), and late-phase receptive (toddlerhood, 24–38 months) vocabulary. Subsequently, we estimated single nucleotide polymorphism-based heritability (SNP- h^2) and genetic correlations (r_g) and modeled underlying factor structures with multivariate models.

RESULTS: Early-life vocabulary size was modestly heritable (SNP- $h^2 = 0.08$ – 0.24). Genetic overlap between infant expressive and toddler receptive vocabulary was negligible ($r_g = 0.07$), although each measure was moderately related to toddler expressive vocabulary ($r_g = 0.69$ and $r_g = 0.67$, respectively), suggesting a multifactorial genetic architecture. Both infant and toddler expressive vocabulary were genetically linked to literacy (e.g., spelling: $r_g = 0.58$ and $r_g = 0.79$, respectively), underlining genetic similarity. However, a genetic association of early-life vocabulary with educational attainment and intelligence emerged only during toddlerhood (e.g., receptive vocabulary and intelligence: $r_g = 0.36$). Increased ADHD risk was genetically associated with larger infant expressive vocabulary ($r_g = 0.23$). Multivariate genetic models in the ALSPAC (Avon Longitudinal Study of Parents and Children) cohort confirmed this finding for ADHD symptoms (e.g., at age 13; $r_g = 0.54$) but showed that the association effect reversed for toddler receptive vocabulary ($r_g = -0.74$), highlighting developmental heterogeneity.

CONCLUSIONS: The genetic architecture of early-life vocabulary changes during development, shaping polygenic association patterns with later-life ADHD, literacy, and cognition-related traits.

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Mastering developmental milestones related to speech and language during the first few years of life shapes later-life development, especially for cognition- and education-related outcomes (1–4), while difficulties acquiring age-appropriate language, communication, and literacy skills have been related to multiple neurodevelopmental conditions (5–10). Consequently, understanding the etiological mechanisms that underlie language development may provide

insight into both early manifestations of cognition and mental health problems.

Language development in infants and toddlers is often assessed with measures of expressive and receptive vocabulary (11,12). These constructs are related to language production and understanding, respectively, and can be ascertained relatively easily (although indirectly) through parental reports. The first spoken words typically emerge

between 10 and 15 months (12). Receptive vocabulary development usually precedes expressive vocabulary development, developing at 6 to 9 months (13). Consequently, the number of words children understand is often larger than the number of words they produce and exceeds the latter by at least 4-fold based on parent reports at 16 months (14). Once children reach an expressive vocabulary size of ~50 words at 12 to 18 months, there is often a period of rapid vocabulary growth from around 16 to 22 months (15), which results in a vocabulary size of 100 to 600 words at 24 months (14). Children typically produce words in isolation during the early phase of language learning (infancy, ≤ 18 months) (12), followed by a phase of more complex language learning that includes 2-word combinations and more complex grammatical structures (14,16). Across early development, there are moderate-to-strong phenotypic correlations (r_p) between parent-assessed measures of vocabulary size at 1-year intervals ($r_p = 0.47\text{--}0.63$) (17,18). However, such correlations tend to decrease with increasing age intervals (18), suggesting phenotypic heterogeneity.

Individual differences in early-life vocabulary development (assessed using parental reports) can be partially explained by genetic factors (17–21). Twin heritability estimates for expressive vocabulary range from 0.10 to 0.25 (24–36 months) (17,19,20) and reflect phenotypic variance accounted for by genome-wide additive genetic influences. These findings are corroborated by single nucleotide polymorphism-based heritability (SNP- h^2) estimates that range from 0.13 to 0.14 (15–30 months) (19) and capture phenotypic variance tagged by single-base variation on genotyping chips. For receptive vocabulary at 14 months, twin heritability was estimated at 0.28 (22). Evidence for SNP- h^2 at a similar age was poor but was present at 38 months (SNP- $h^2 = 0.12$) (18).

Population-based studies of language development spanning infancy to early childhood in English-speaking children (reported by parents) have revealed a complex underlying genetic architecture, with evidence for both stability and change (17–19,23). Genetic correlations (r_g), indicating shared genetic influences between 2 phenotypes, have ranged from 0.48 to 0.74 for expressive vocabulary measures between 15 and 38 months (17–19), suggesting moderate-to-strong genetic stability. At the individual SNP level, our group identified a genome-wide signal for early-life vocabulary (rs7642482 near *ROBO2*) as part of a previous meta-genome-wide association study (meta-GWAS) ($N = 8889$) (19). rs7642482 is associated with expressive vocabulary in infants (age: 15–18 months), but the signal is attenuated in toddlers (age: 24–30 months) (19), suggesting that age-specific genetic mechanisms contribute to phenotypic heterogeneity.

Similar to phenotypic observations (1–4), genetic influences that underlie early-life vocabulary are shared with many later language and literacy abilities. In UK twins, for example, parent-assessed early expressive language skills (24–48 months) were moderately genetically correlated ($r_g = 0.36$) with teacher-assessed childhood reading abilities (23). Similarly, in a UK population-based genomic study, parent-assessed receptive vocabulary size (38 months) showed moderate-to-strong genetic correlations ($r_g = 0.58\text{--}0.92$) with mid-childhood reading task performance (24). However, genetic links of infant and toddler vocabulary size with cognition-

related skills beyond mid-childhood are not fully understood and could provide insight into the early manifestations underlying cognitive functioning during later periods of development.

Early-life vocabulary performance may also impact subsequent behavioral and health outcomes, including childhood-onset neurodevelopmental conditions such as attention-deficit/hyperactivity disorder (ADHD) (5–8) and autism spectrum disorder (9,10). For example, poor language skills at 3 years were predictive of inattention and hyperactive symptoms 2 years later (8), and higher ADHD risk has been genetically related to poorer reading performance (25–28). For children diagnosed with autism spectrum disorder, the phenotypic spectrum is broader, including both children with few language problems and children with little or no spontaneous spoken language by the time they reach school age (9,10). However, genetic relationships between risk for neurodevelopmental conditions and early-life, population-based vocabulary measures remain largely uncharacterized. Furthermore, progress in mastering language abilities may implicate brain growth as captured with phenotypic proxies such as head circumference (29), which shows strong correlations with brain volume (30,31).

In this meta-GWAS study, we investigated genetic influences underlying early-life vocabulary acquisition and assessed genetic overlap with literacy, general cognition, developmental phenotypes, and childhood-onset neurodevelopmental conditions. This work builds on our previous GWAS effort investigating infant and toddler expressive vocabulary (19) by increasing the number of children studied by ~50% and adopting a multivariate analysis approach to maximize statistical power. Furthermore, we extended the phenotypic spectrum by including both expressive and receptive vocabulary size and examined developmental changes in underlying common genetic contributions at both the single-variant and genomic trait covariance level. The developmental windows that were studied include an early, single-word phase (15–18 months, infancy) and a late phase during which children start using 2-word combinations and more complex grammatical structures (24–38 months, toddlerhood).

METHODS AND MATERIALS

Phenotype Selection and Study Design

Cohorts with quantitative vocabulary scores assessed during the first 3 years of life and genome-wide genotypes were invited to participate in this study (17,298 independent children of European descent, 37,913 parent-reported vocabulary size measures), embedded within the EAGLE (Early Genetics and Life Course Epidemiology) Consortium (32) (<https://www.eagle-consortium.org/working-groups/behaviour-and-cognition/early-language/>). Expressive vocabulary scores were assessed at 15 to 38 months and analyzed across 2 developmental phases to allow for age-specific genetic influences: an early phase (15–18 months, infancy) and a late phase (24–38 months, toddlerhood). Scores for receptive vocabulary were included for the late phase only given low validity (33,34), low SNP- h^2 (18), and limited data availability for early-phase measures (Supplemental Methods).

Genome-wide Analyses of Infant and Toddler Vocabulary

Up to 7 population-based cohorts participated in this study (Figure 1; Table S1; Supplemental Methods), 2 of which had longitudinal vocabulary assessments (Tables S2, S3). Vocabulary scores were ascertained by parental report using age-specific (adapted) word lists from the MacArthur Communicative Development Inventory (CDI) (20,35–39) or the Language Development Survey (40) (Supplemental Methods; Table S1). The CDI is a widely used psychological instrument to assess children's vocabulary development and is available in more than 60 languages (41). Cross-linguistic comparisons showed similar trends of early vocabulary development across multiple languages, including English, Dutch, and Danish (41). However, the exact number of words produced and understood may differ across languages (42,43), making CDI score standardization necessary. The CDI and Language Development Survey have been validated extensively (39,44–47). Both instruments have high concurrent validity for children's vocabulary at 23 to 25 months (intercorrelation of scores: 0.95) (48), and have low measurement error (49) (Supplemental Methods).

Ethical approval was obtained by the local research ethics committee for each participating study, and all parents and/or legal guardians provided written informed consent (Supplemental Methods).

Genotyping and Imputation

Genotyping was conducted using high-density SNP arrays within each cohort, and quality control followed standard procedures (50) (Table S4). In total, between 440,476 and 608,517 high-quality autosomal genotyped markers were

imputed against the HRC (Haplotype Reference Consortium) r1.1 panel (51) (Table S4).

Single-Variant Association Analyses and Meta-analyses

Within each cohort, vocabulary scores were adjusted for age, sex, age², and their interaction effects, as well as ancestry-informative principal components and study-specific covariates, such as genotyping array and/or batch, and rank-transformed to achieve normality and allow for comparisons of genetic association effects across different psychological instruments. SNP-vocabulary associations were then estimated within each cohort using linear regression of rank-transformed residuals on posterior genotype probability, assuming an additive genetic model and using SNPTTEST (52), Probel (53), or GEMMA (54) software, except for the LSAC (Longitudinal Study of Australian Children) cohort. In the LSAC sample, best-guess genotypes were analyzed assuming an additive genetic model using PLINK version 1.9 (55) (Supplemental Methods). Prior to meta-analysis, GWAS summary statistics underwent extensive quality control using the EasyQC R-package (version 9.2) (56) (Table S4; Supplemental Methods).

In stage I, single-trait meta-analyses were performed for early-phase expressive, late-phase expressive, and late-phase receptive vocabulary using METAL (57) and/or MTAG software (58). In stage II, multitrait meta-analyses across genetically correlated scores were carried out with MTAG software to increase statistical power while allowing for sample overlap (58) (Figure 1; Supplemental Methods).

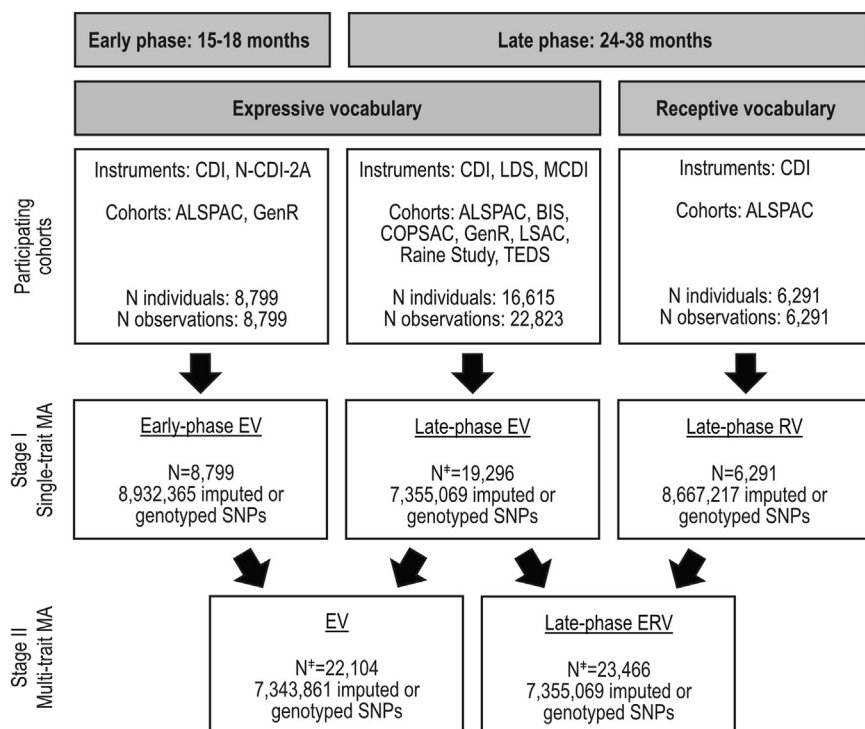


Figure 1. Study design. Vocabulary size was assessed between 15 and 38 months and studied with respect to an early-phase (15–18 months, infancy) and late-phase (24–38 months, toddlerhood) developmental window of language acquisition to allow for age-specific genetic influences. Scores for receptive vocabulary were included in the late-phase window only. In stage I, 3 single-trait MAs were conducted: early-phase expressive vocabulary, late-phase expressive vocabulary, and late-phase receptive vocabulary. In stage II, multitrait genome-wide analyses were performed across early-phase and late-phase expressive vocabulary, as well as across late-phase expressive and receptive vocabulary to increase statistical power. *Estimated sample size based on the increase in mean χ^2 statistic using MTAG software. ALSPAC, Avon Longitudinal Study of Parents and Children; BIS, Barwon Infant Study; CDI, Communicative Development Inventory; COPSAC, Copenhagen Prospective Studies on Asthma in Childhood; ERV, expressive and receptive vocabulary; EV, expressive vocabulary; GenR, Generation R Study; LDS, Language Development Survey; LSAC, Longitudinal Study of Australian Children; MA, meta-analysis; MTAG, multitrait analysis of genome-wide association; RV, receptive vocabulary; SNP, single nucleotide polymorphism; TEDS, Twins Early Development Study.

The number of independent vocabulary measures in this study was 2.38 as estimated with matSpD (59) software based on genetic correlations (see below), corresponding to a multiple-testing adjusted genome-wide association significance threshold of $p < 2.10 \times 10^{-8}$ ($5 \times 10^{-8}/2.38$).

FUMA Analyses

SNP-vocabulary associations that passed the unadjusted genome-wide significance threshold ($p < 5 \times 10^{-8}$) were identified and annotated using FUMA (version 1.3.6) (60). Additionally, gene-based genome-wide, gene-set, and gene-property analyses were conducted with MAGMA (version 1.08) (61) software within FUMA (version 1.3.6a) (60) (Supplemental Methods).

SNP- h^2 and Genetic Relationship Analyses

SNP- h^2 was estimated for all derived vocabulary GWAS summary statistics (stages I and II) and preselected traits for genetic relationship analyses (see below) using high-definition likelihood (HDL) (62) (Supplemental Methods). HDL adjusts for inherent sample overlap and estimates SNP- h^2 and r_g with increased accuracy compared to linkage disequilibrium (LD) score regression analyses (62). To confirm the robustness of HDL results, SNP- h^2 was also estimated using LD score regression (63) for vocabulary summary statistics.

To ensure sufficient power for HDL- r_g analyses, we selected traits with HDL-SNP- h^2 ($p < .05$) and HDL-SNP- h^2 z score ≥ 4 (64) (Supplemental Methods). We assessed genetic overlap 1) among single-trait vocabulary measures (stage I) and 2) across single-trait vocabulary measures (stage I) and several preselected GWAS summary statistics, including literacy-related phenotypes such as word reading (65) (5–26 years, $N = 27,180$), nonword reading (65) (5–26 years, $N = 16,746$), spelling (65) (5–26 years, $N = 17,278$), and phoneme awareness (65) (5–18 years, $N = 12,411$); general cognition-related phenotypes such as intelligence (66) (5–98 years, $N = 279,930$) and educational attainment (67) (>30 years, $N = 766,345$); proxy measures of brain growth such as infant head circumference (68) (6–30 months, $N = 10,768$) and childhood head circumference (69) (6–9 years, $N = 10,600$); childhood behavior such as aggressive behavior (70) (1.5–18 years, $N = 151,741$) and internalizing symptoms (71) (3–18 years, $N = 64,641$); as well as childhood-onset neurodevelopmental conditions such as ADHD (72) ($N = 53,293$; $n_{\text{cases}} = 19,099$) and autism spectrum disorder (73) ($N = 46,350$; $n_{\text{cases}} = 18,381$). The multiple-testing adjusted threshold for HDL- r_g analyses was $p < 5.57 \times 10^{-3}$, reflecting 8.98 independent traits as estimated using matSpD (59,74) and a bivariate genetic correlation matrix (Figure S1).

Given limited data availability, modest SNP- h^2 , and relatively low sample sizes, polygenic prediction of independent vocabulary measures was either not possible or underpowered (Supplemental Note).

Structural Equation Modeling

To study covariance patterns of ADHD symptoms with early-life vocabulary size, we modeled the underlying multivariate genetic and residual structure using a structural equation modeling (SEM) approach based on individual data (genetic-relationship matrix SEM [GRM-SEM]) (grmsem, version 1.1.2) (75) (Supplemental Methods). Note that it is not possible to

model residual (i.e., joint environmental, nonadditive genetic, and error) influences with summary statistic-based SEM frameworks such as Genomic SEM (76). Individual-level data were obtained from unrelated children ($N \leq 6524$) in the ALSPAC (Avon Longitudinal Study of Parents and Children) cohort (77,78); measures of vocabulary size were identical to those included in the meta-GWAS (Table S1), and ADHD symptom scores were assessed with the Strengths and Difficulties Questionnaire (79) based on teacher and mother reports (7–17 years). For both report types, ADHD symptoms with the highest SNP- h^2 z scores were selected for subsequent analyses (Supplemental Methods; Table S5).

Given the temporal order of studied traits, we fitted a GRM-SEM Cholesky decomposition model (80) to the data. A Cholesky decomposition dissects the phenotypic covariance structure into additive genetic factors (A), which capture genetic variance tagged by common genotyped SNPs (75), and residual factors (E), which reflect all other sources of variance, including error. The Cholesky decomposition model is a saturated model with as many latent genetic and residual factors as there are observed variables, without any restrictions on the structure (80). Subsequently, genetic and residual correlations (r_a) were estimated according to theory (81) using grmsem (version 1.1.2) (75). Phenotypic correlations (r_p) were derived using Pearson correlation in R (R:stats library, version 4.1.0).

RESULTS

Single-Trait and Multitrait Meta-GWAS

Single-trait genome-wide association analyses were carried out for early-phase expressive (15–18 months, $N = 8799$), late-phase expressive (24–38 months, $N = 16,615$), and late-phase receptive (24–38 months, $N = 6291$) vocabulary size (stage I, Figure 1) using data from English-, Dutch-, or Danish-speaking children of European descent, combining up to 7 independent cohorts (Table S1). There was little evidence for novel SNP signals at the multiple-testing-adjusted genome-wide significance level ($p < 2.10 \times 10^{-8}$) (Figures S2A–C). For early-phase expressive vocabulary, a single GWAS signal passed the unadjusted genome-wide significance threshold (rs9854781, $p < 5 \times 10^{-8}$), consistent with a known locus identified through a previous meta-GWAS studying overlapping samples (rs764282, LD $r^2 = 0.78$) (19). Genome-wide gene-based, gene-set, and gene-property analyses did not provide evidence for association that passed the multiple-testing-adjusted significance thresholds (Figure S3; Table S6).

All early-life vocabulary measures were modestly heritable, with SNP- h^2 estimates of 0.24 (SE = 0.02), 0.08 (SE = 0.01), and 0.20 (SE = 0.04) for early-phase expressive vocabulary, late-phase expressive vocabulary, and late-phase receptive vocabulary, respectively (Figure 2A; Table S7). Genetic correlations between early- and late-phase expressive vocabulary ($r_g = 0.69$ [SE = 0.14]) and between late-phase expressive and receptive vocabulary ($r_g = 0.67$ [SE = 0.16]) were moderate (Figure 2B), suggesting some stability in genetic factors during development. However, genetic influences underlying early-phase expressive vocabulary were largely independent of those related to late-phase receptive vocabulary ($r_g = 0.07$ [SE = 0.10]). Given similar power to detect genetic overlap with

Genome-wide Analyses of Infant and Toddler Vocabulary

late-phase receptive vocabulary using either expressive score ($r_g = 0.70$, statistical power: early-phase expressive vocabulary = 83%, late-phase expressive vocabulary = 71%), these findings suggest developmental genetic heterogeneity and the existence of multiple genetic factors.

To maximize statistical power for single-variant discovery, we combined genetically correlated vocabulary measures (i.e., early- and late-phase expressive vocabulary and late-phase expressive and receptive vocabulary) (Figure 2B) as part of 2 multitrait meta-analyses using MTAG (stage II, Figure 1). However, neither measure identified further SNP-vocabulary associations (Figures S2D, E; Table S8), nor did we find increased evidence for SNP- h^2 (z scores, Table S7). Thus, subsequent analyses were restricted to stage I vocabulary summary statistics only.

Genetic Relationships With Cognition-, Development-, and Health-Related Outcomes

We investigated genetic links between early-life vocabulary measures (stage I) and several preselected heritable cognition-, development-, and health-related outcomes (see Table S9 for SNP- h^2) by estimating genetic correlations using HDL software (62) (multiple-testing-adjusted threshold: $p < 5.57 \times 10^{-3}$). Consistent with the estimated genetic architecture underlying early-life vocabulary size (see above), genetic correlation patterns were consistent with a multifactorial genetic architecture (Figure 3; Table S10).

Both infant and toddler expressive vocabulary were genetically linked to literacy-related measures, most strongly to spelling ($r_g = 0.58$ [SE = 0.20] and $r_g = 0.79$ [SE = 0.25], respectively), and, for late-phase expressive vocabulary only, word reading ($r_g = 0.61$ [SE = 0.17]). These findings strengthen the evidence for shared genetic factors contributing to expressive vocabulary size during early-life language development.

However, genetic correlation patterns with general cognition-related phenotypes differed for infant versus toddler

vocabulary size (Figure 3) despite comparable study power across developmental phases (Table S11). Associations emerged in toddlerhood, when larger late-phase expressive and receptive vocabulary size were genetically correlated with higher intelligence across the life span (late-phase expressive vocabulary: $r_g = 0.32$ [SE = 0.08]; late-phase receptive vocabulary: $r_g = 0.36$ [SE = 0.12]) and with higher adult educational attainment (late-phase expressive vocabulary: $r_g = 0.26$ [SE = 0.05]; late-phase receptive vocabulary: $r_g = 0.37$ [SE = 0.06]). For the latter, 95% confidence intervals do not overlap with those for correlation estimates between educational attainment and early-phase expressive vocabulary, supporting the presence of developmental genetic change from infancy to toddlerhood (Table S10).

Genetic association patterns of vocabulary size with childhood behavior-related traits and neurodevelopmental conditions, especially ADHD, also changed during development (Figure 3). While larger early-phase expressive vocabulary size was genetically correlated with increased ADHD risk ($r_g = 0.23$ [SE = 0.08]), this genetic correlation was attenuated for both late-phase vocabulary measures (Figure 3). To explore the genetic association pattern with ADHD in detail, we studied individual-level data from children in the ALSPAC cohort using GRM-SEM (75). Within ALSPAC, we dissected the phenotypic covariance of 4 early-life vocabulary measures (expressive vocabulary at 15, 24, and 38 months; receptive vocabulary at 38 months) and ADHD symptoms (8 and 13 years) (Table S5) into 6 independent genetic (A) and 6 independent residual (E) factors in temporal order by fitting a saturated (Cholesky) structural model (Figure 4A; Table S12). Confirming summary statistic-based findings (Figure 3), larger early-phase expressive vocabulary (15 months) was genetically correlated with more ADHD symptoms ($r_{g_ADHD8y} = 0.56$ [SE = 0.26]; $r_{g_ADHD13y} = 0.54$ [SE = 0.25]) (Figure 4B). This association was captured by the first genetic factor, A1, with positive factor loadings (λ) for early-phase expressive vocabulary and ADHD symptoms at 8 and 13 years ($\lambda_{EV15m} = 0.34$ [SE = 0.07];

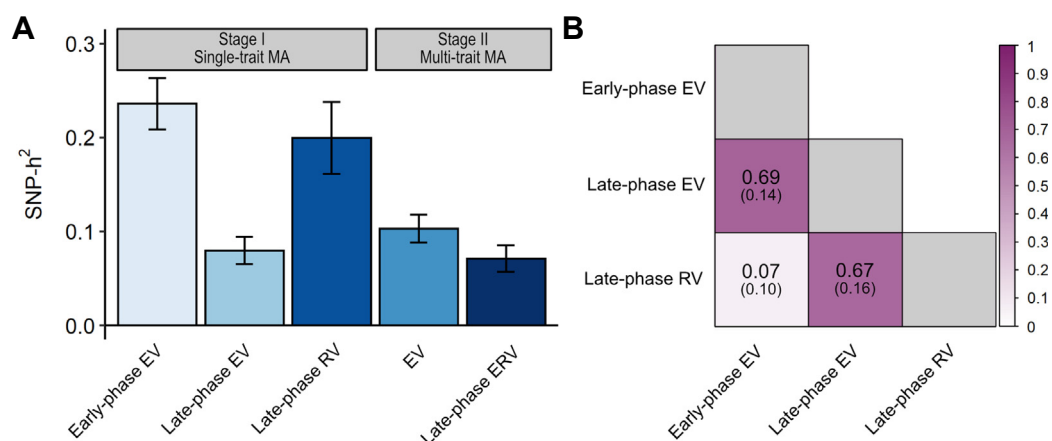


Figure 2. SNP- h^2 and genetic correlations for infant and toddler vocabulary size. (A) SNP- h^2 estimates for single- and multitrait vocabulary summary statistics were estimated with HDL software (62). Error bars represent standard errors. (B) Genetic correlations (r_g) between single-trait vocabulary summary statistics were estimated with HDL software (62). Corresponding standard errors are shown in brackets. EV, expressive vocabulary; ERV, expressive and receptive vocabulary; HDL, high-definition likelihood; MA, meta-analyses; RV, receptive vocabulary; SNP- h^2 , single nucleotide polymorphism-based heritability.

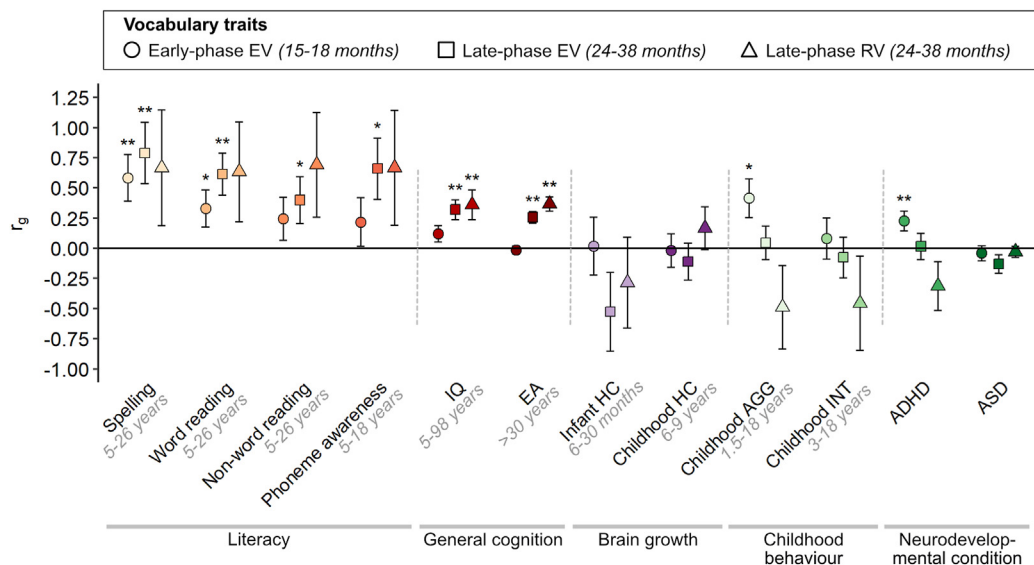


Figure 3. Genetic correlations of vocabulary size with cognition-, development-, and health-related outcomes. Genetic correlations were estimated with HDL (62) software. Error bars represent standard errors. * $p < .05$, **multiple-testing adjusted $p < 5.57 \times 10^{-3}$. ADHD, attention-deficit/hyperactivity disorder; AGG, aggression; ASD, autism spectrum disorder; EA, educational attainment; EV, expressive vocabulary; HC, head circumference; HDL, high-definition likelihood; INT, internalizing symptoms; r_g , genetic correlation; RV, receptive vocabulary.

$\lambda_{ADHD8y} = 0.28$ [SE = 0.13]; $\lambda_{ADHD13y} = 0.27$ [SE = 0.12] (Figure 4A). In contrast, we observed an inverse genetic correlation between larger late-phase receptive vocabulary size (38 months) and lower ADHD symptoms ($r_{g_ADHD8y} = -0.60$ [SE = 0.23]; $r_{g_ADHD13y} = -0.74$ [SE = 0.16]) (Figure 4B). This inverse genetic association was captured by 2 independent genetic factors, A2 and A4 (Figure 4A). A2 reflects genetic influences underlying expressive vocabulary size at 24 months ($\lambda_{EV24m} = 0.33$ [SE = 0.06]) that, independent of A1, were inversely linked to ADHD symptoms ($\lambda_{ADHD8y} = -0.41$ [SE = 0.11]; $\lambda_{ADHD13y} = -0.25$ [SE = 0.12]). A4 explained unique genetic variance contributing to receptive vocabulary size at 38 months ($\lambda_{RV38m} = 0.15$ [SE = 0.08], although this effect did not pass the conventional level of significance with $p = .07$) and was inversely associated with ADHD symptoms at 13 years ($\lambda_{ADHD13y} = -0.34$ [SE = 0.14]). Thus, the Cholesky-estimated genetic factor structure captured opposite association patterns for ADHD symptoms in relation to early-phase (infancy) versus late-phase (toddlerhood) vocabulary measures (Figure 4A; Table S12).

Finally, we compared phenotypic and Cholesky-derived genetic and residual correlations between early-life vocabulary size and ADHD symptoms in the ALSPAC sample. While genetic, residual, and phenotypic correlations had the same direction of effect for all 3 late-phase vocabulary measures (Figure 4B–D), we uncovered a rare violation of Cheverud’s conjecture (82) in infancy. Cheverud’s conjecture postulates that phenotypic correlations are likely to be fair estimates of their genetic counterparts (82). In infancy, however, the positive genetic association between early-phase expressive vocabulary and ADHD symptoms ($r_{g_ADHD8y} = 0.56$ [SE = 0.26]) was masked at the phenotypic level ($r_{p_ADHD8y} = -0.06$ [SE = 0.02]) by a negative residual correlation ($r_{e_ADHD8y} = -0.19$ [SE = 0.06]), as was shown here for ADHD symptoms at 8

years. This suggests that the relationship between ADHD symptoms and early-life vocabulary size is subject to etiological changes that are likely to implicate both genetic and nongenetic factors.

DISCUSSION

This meta-GWAS of expressive and receptive vocabulary size in infancy and toddlerhood identified marked differences in genetic influences contributing to vocabulary measures at different developmental phases. The genetic heterogeneity across early-life vocabulary size matched distinct polygenic association patterns with ADHD, literacy, and cognition-related traits. These findings implicate dynamic and rapid changes in the genetic architecture of vocabulary acquisition across a period of less than 2 years. Specifically, they underline the importance of adopting a developmental perspective when studying the biology underlying early-life vocabulary development and shared links with neurodevelopmental conditions.

Bivariate genetic correlation patterns and multivariate structural models in our study suggested at least 2 independent genetic factors contributing to early-life vocabulary size, confirming previous reports of a heterogeneous genetic architecture (17–19,23). Genetic influences that contribute to utterances in infancy, approximated here by early-phase expressive vocabulary size (15–18 months), may capture the first stages of emerging speech during language learning. During this phase of “learning to speak,” words are usually produced in isolation (12). More specifically, children not only acquire phonological skills to identify phonemes and sequences from speech and store them for future production (83) but also develop oral motor (84) and speech motor skills (85). These processes are likely to start during infancy but may impact later reading and spelling abilities (86,87), consistent

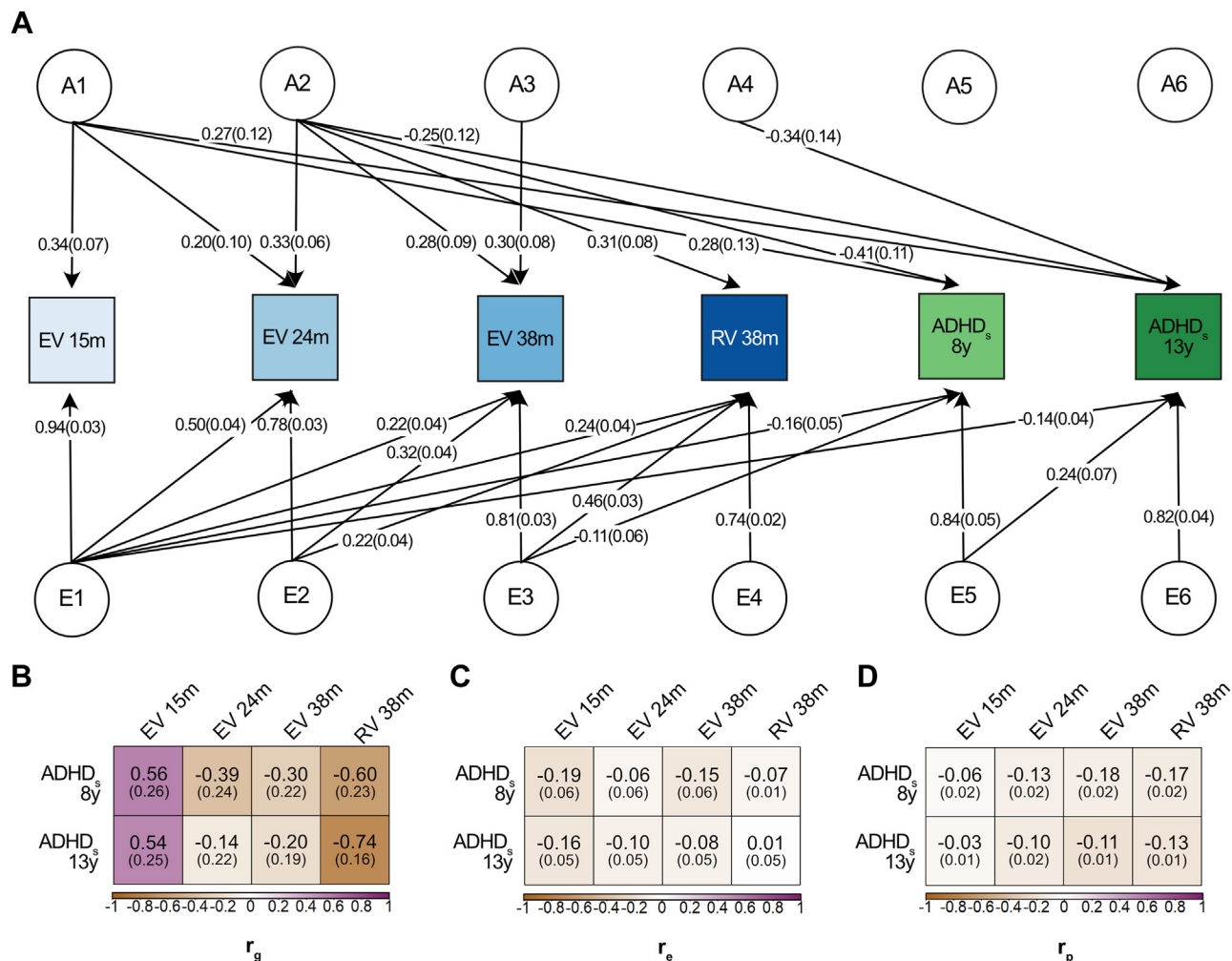


Figure 4. Cholesky decomposition of early-life vocabulary size and later ADHD symptoms. Genetic-relationship matrix structural equation modeling of vocabulary scores (15, 24, and 38 months) in combination with ADHD symptom scores (teacher report at 8 years and mother report at 13 years) based on all available observations for children across development ($N \leq 6524$). Individual-level data were retrieved from the ALSPAC cohort. **(A)** Path diagram with standardized factor loadings and corresponding standard errors for a Cholesky decomposition. Observed measures are represented by squares and latent factors by circles. Single-headed arrows (paths) define relationships between variables. Only paths with a factor loading of $p < .05$ are shown. The variance of latent factors is constrained to unit variance; this is omitted from the diagram to improve clarity. Full information on all factor loadings and their standard errors can be found in Table S12. **(B)** Genetic, **(C)** residual, and **(D)** phenotypic correlation patterns between early-life vocabulary size and ADHD symptom scores assessed at 8 and 13 years. Genetic and residual correlations were estimated with genetic-relationship matrix structural equation modeling (75) based on a Cholesky decomposition model [shown in **(A)**]. Phenotypic correlations were estimated with Pearson correlations. Standard errors are shown in parentheses. ALSPAC, Avon Longitudinal Study of Parents and Children; ADHD, attention-deficit/hyperactivity disorder; ADHD_s, ADHD symptom scores; EV, expressive vocabulary; r_e , residual correlation; r_g , genetic correlation; r_p , phenotypic correlation; RV, receptive vocabulary.

with genetic correlations of both early- and late-phase expressive vocabulary with literacy-related phenotypes observed in this study.

Genetic associations with educational attainment and general intelligence were only detectable for late-phase vocabulary scores during toddlerhood (24–38 months), consistent with previous research (18). Despite sufficient statistical power ($>90\%$ power to detect $r_g \geq 0.20$ with educational attainment), there was little evidence for shared genetic effects with early-phase vocabulary scores. Thus, the genetic overlap of toddler expressive and receptive vocabulary with general cognition-related measures may reflect the onset of a subsequent phase of “speaking to learn.” During this phase, toddlers

have mastered some language fluency and start to use word combinations and more complex grammatical structures (14,16), requiring higher-level cognitive processing.

Heterogeneity in genetic components that contribute to early-life vocabulary size was also reflected by distinct polygenic association patterns with later-life behavioral traits and neurodevelopmental conditions, especially ADHD. During infancy, larger expressive vocabulary was associated with both an increased polygenic risk for ADHD and ADHD symptoms as captured by meta-GWAS summary statistics and individual-level multivariate analyses in ALSPAC, respectively. This is consistent with a previous ALSPAC study that found a positive genetic association between infant gross motor skills and

polygenic ADHD risk (88). Younger age at first walking was consistently linked to higher polygenic ADHD load in an independent, large Norwegian population-based cohort (89). Thus, during a developmental phase of “learning to speak,” when motor skills shape children’s learning environment and, in turn, behavior and language learning (90), children with a higher genetic predisposition for ADHD may be genetically inclined to express a larger rather than a smaller vocabulary size. In contrast, the polygenic relationship with ADHD symptoms reversed for receptive vocabulary in toddlerhood, as was observed in ALSPAC, consistent with known genetic associations between higher ADHD risk and lower child and adolescent verbal and cognitive abilities (28). Structural models showed that a genetic factor specifically capturing toddlerhood vocabulary measures (i.e., beyond variation in infant vocabulary) was inversely associated with ADHD symptom expression. Therefore, for phenotypes such as late-phase expressive vocabulary, which shares genetic influences with both early-phase expressive and late-phase receptive vocabulary, positive and negative genetic covariance patterns with ADHD symptoms may cancel each other out, consistent with little evidence for a genome-wide genetic correlation.

However, genetic and residual contributions to phenotypic correlations of early-life vocabulary size with ADHD symptoms are complex. Positive genetic associations of early-phase expressive vocabulary with ADHD symptoms (see Figure 4) were masked at the phenotypic level due to residual correlations with an opposite direction of effect. This rare violation of Cheverud’s conjecture (82) suggests that residual sources of variation do not affect developmental pathways in the same way as genetic sources and may implicate a protective effect of the caregiving environment as observed for some behavioral traits in animals (91). Thus, despite the validity of Cheverud’s conjecture in general (92), future research characterizing the divergent genetic and residual association patterns in very young children may require information on parental language input.

This work has several strengths and limitations. First, our work builds on a previous GWAS effort (19) by increasing the number of children studied by ~50%. The derived summary statistics captured a substantial fraction of phenotypic variance and had $\text{SNP-}h^2$ z scores ≥ 4 , enabling genome-wide genetic covariance analyses (64). Therefore, the current work could capture genetic association patterns for cognition-related traits and neurodevelopmental conditions, especially ADHD. However, the power to detect single-variant contributions of small effect (e.g., 0.1%) remained low (Supplemental Note). Second, the use of HDL software boosted the power of genetic correlation analyses (62). Summary statistic-based SEM approaches using HDL [e.g., genomic SEM (76)] could not be used due to limited overlap with recommended genetic reference panels. Therefore, multivariate genomic and residual covariance patterns were modeled with GRM-SEM (75), studying individual-level data within the ALSPAC cohort. Third, our study exclusively focused on children of European genetic ancestry, combining cohorts representing 3 different European languages that showed comparability on CDI measures (42,43), which boosted study power. Due to recent methodological advances (93,94), transancestry genetic meta-analysis will become more feasible in the future. However,

transancestral studies of early language development are complex because vocabulary acquisition processes may differ across language families. For example, word learning in noun-friendly languages (e.g., English) differs from that in verb-friendly languages (e.g., Korean) (95), and linguistic differences may become confounded with genetic ancestry. Fourth, all language measures were rank-transformed to harmonize vocabulary measures across different developmental phases, languages, and instruments. Although we cannot exclude bias, it is unlikely that this data transformation affected the nature of our findings considering robust phenotypic relationships across untransformed and transformed vocabulary scores studied in previous work (18). Fifth, children’s language development encompasses a broad range of genetically related phenotypes in addition to vocabulary size, such as grammatical abilities (17,20). Joint analysis of such interrelated skills, especially with longitudinal measures, may boost study power as part of future meta-GWASs and enable the study of vocabulary growth. Finally, given differences in vocabulary acquisition for boys and girls (43), future work studying more powerful samples may uncover sex-specific differences in genetic contributions to language development.

Conclusions

In summary, there are at least 2 genetic factors that contribute to vocabulary size during infancy and toddlerhood matching distinct polygenic association patterns with several later-life traits. Our findings highlight the importance of studying genetic influences that underlie early-life vocabulary acquisition to unravel etiological processes shaping future behavior and cognition.

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Genome-wide Analyses of Infant and Toddler Vocabulary

EAGLE Working Group report that the EAGLE Working Group is one of the named authors and that all members qualify for authorship.

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Derived single-trait (stage I) and multitrait (stage II) vocabulary summary statistics will be made available upon publication of the article via a data repository. EV and BSP had full access to all summary statistic-level data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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ARTICLE INFORMATION

From the Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands (EV, EE, MO, FS, SEF, BSP); Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (AGA, KR, SS, RP); Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Rotterdam, the Netherlands (PRJ, HT, CAMC); Department of Complex Trait Genetics, Center for Neurogenetics and Cognitive Research, Amsterdam Neuroscience, Vrije Universiteit, Amsterdam, the Netherlands (PRJ); Section Clinical Genetics, Department Human Genetics, Amsterdam University Medical Centers, Amsterdam, the Netherlands (PRJ); Murdoch Children's Research Institute, Parkville, Victoria, Australia (KL, ATM, CS, TM, EO, RS, SR, MW); Department of Paediatrics, University of Melbourne, Parkville, Victoria, Australia (KL, ATM, TM, RS, SR, MW); School of Medicine and Public Health, The University of Newcastle, Newcastle, New South Wales, Australia (CAW, CEP); Mothers and Babies Research Program, Hunter Medical Research Institute, Newcastle, New South Wales, Australia (CAW, CEP); Department of Audiology and Speech Pathology, University of Melbourne, Parkville, Victoria, Australia (ATM); Royal Children's Hospital, Melbourne, Victoria, Australia (ATM, CS); Copenhagen Prospective Studies on Asthma in Childhood, Herlev and Gentofte Hospital, University of Copenhagen, Copenhagen, Denmark (TSA, KB); Steno Diabetes Center Copenhagen, Herlev, Denmark (TSA); Bioinformatics Center, Department of Biology, University of Copenhagen, Copenhagen, Denmark (TSA); Minderoo Foundation, Perth, Western Australia, Australia (CS); Erasmus University Medical Center, Sophia Children's Hospital, Department of Otorhinolaryngology and Head and Neck Surgery, Rotterdam, the Netherlands (M-CF); Australian Centre for Precision Health, Unit of Clinical and Health Sciences, University of South Australia, Adelaide, South Australia, Australia (EH); South Australian Health and Medical Research Institute (EH), Adelaide, South Australia, Australia; Department of Urology, Erasmus University Medical Center, Erasmus University Medical Center Cancer Institute, Rotterdam, the Netherlands (MO); Department of Psychology, Royal Holloway University of London, London, UK (KR); Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, UK (CYS, BSP); Population Health Sciences, University of Bristol, Bristol, UK (CYS); Harvard, T.H. Chan School of Public Health, Boston, Massachusetts (HT); Telethon Kids Institute, The University of Western Australia, Perth, Western Australia, Australia (AJOW); Chongqing Medical University, Chongqing, China (RS); Menzies Health Institute Queensland, Griffith University, Brisbane, Queensland, Australia (SR); Maternity and Gynaecology John Hunter Hospital, Newcastle, New South Wales, Australia (CEP); Liggins Institute, The University of Auckland, Grafton, New Zealand (MW); Department of Epidemiology, Erasmus University Medical Center, Rotterdam, the Netherlands (CAMC); Molecular Epidemiology, Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, the Netherlands (CAMC); and Donders Institute for

Brain, Cognition and Behaviour, Radboud University, Nijmegen, the Netherlands (SEF, BSP).

The EAGLE Working Group that contributed to this manuscript consists of the following members: Ole A. Andreassen (1,2,3), Meike Bartels (4), Dorret Boomsma (4), Philip S. Dale (5), Erik Ehli (6), Dietmar Fernandez-Orth (7), Mònica Guxens (7,8,9,10), Christian Hakulinen (11), Kathleen Mullan Harris (12,13), Simon Haworth (14,15), Lucia de Hoyos (16), Vincent Jaddoe (17,18), Liisa Keltikangas-Järvinen (19), Terho Lehtimäki (20,21,22), Christel Middeldorp (23,24), Josine L. Min (14,25), Pashupati P. Mishra (20,21,22), Pål Rasmus Njolstad (26,27), Jordi Sunyer (7,8,9), Ashley E. Tate (28), Nicholas Timpson (14,25), Camiel van der Laan (4), Martine Vrijheid (7,8,9), Eero Vuoksima (29), Alyce Whipp (29), Eivind Ystrom (30,31), ACTION Consortium (32), Barwon Infant Study investigator group (33).

(1) Norwegian Centre for Mental Disorders Research, Institute of Clinical Medicine, University of Oslo, Oslo, Norway; (2) Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; (3) KG Jebsen Centre for Neurodevelopmental disorders, University of Oslo, Oslo, Norway; (4) Netherlands Twin Register, dept Biological Psychology, Vrije Universiteit Amsterdam, the Netherlands; (5) Speech & Hearing Sciences Department, University of New Mexico, Albuquerque, New Mexico; (6) Avera Institute for Human Genetics, Sioux Falls, South Dakota; (7) ISGlobal, Barcelona, Spain; (8) Universitat Pompeu Fabra, Barcelona, Spain; (9) Spanish Consortium for Research on Epidemiology and Public Health, Instituto de Salud Carlos III, Madrid, Spain; (10) Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, University Medical Center, Rotterdam, the Netherlands; (11) Department of Psychology and Logopedics, University of Helsinki, Finland; (12) Department of Sociology, University of North Carolina at Chapel Hill, North Carolina; (13) Carolina Population Center, University of North Carolina at Chapel Hill, North Carolina; (14) Medical Research Council Integrative Epidemiology Unit at the University of Bristol, Bristol, England, UK; (15) Bristol Dental School, University of Bristol, Bristol, England, UK; (16) Language and Genetics Department, Max Planck Institute for Psycholinguistics, Nijmegen, the Netherlands; (17) Department of Pediatrics, Erasmus University Medical Center, Rotterdam, the Netherlands; (18) Generation R Study Group, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands; (19) Faculty of Medicine, University of Helsinki, Helsinki, Finland; (20) Department of Clinical Chemistry, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; (21) Finnish Cardiovascular Research Centre, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; (22) Department of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland; (23) University of Queensland, Child Health Research Centre, Brisbane, Queensland, Australia; (24) Child and Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, Brisbane, Queensland, Australia; (25) Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK; (26) Department of Clinical Science, University of Bergen, Bergen, Norway; (27) Children and Youth Clinic, Haukeland University Hospital, Bergen, Norway; (28) Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden; (29) Institute for Molecular Medicine Finland, HiLIFE, University of Helsinki, Helsinki, Finland; (30) PROMENTA Research Center, Department of Psychology, University of Oslo, Oslo, Norway; (31) Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway; (32) Supplemental Note, ACTION Consortium Genome-wide-Association Meta-analysis authors and affiliations; (33) Supplemental Note, Barwon Infant Study investigator group authors and affiliations.

Address correspondence to Beate St. Pourcain, Ph.D., at Beate.StPourcain@mpi.nl, or Ellen Verhoef, Ph.D., at ellen.verhoef@mpi.nl.

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