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Genetics of early-life head circumference and genetic correlations with neurological, psychiatric and cognitive outcomes

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Abstract

Background: Head circumference is associated with intelligence and tracks from childhood into adulthood.

Methods: We performed a genome-wide association study meta-analysis and follow-up of head circumference in a total of 29,192 participants between 6 and 30 months of age.

Results: Seven loci reached genome-wide significance in the combined discovery and replication analysis of which three loci near *ARFGF2*, *MYCL1*, and *TOP1*, were novel. We observed positive genetic correlations for early-life head circumference with adult intracranial volume, years of schooling, childhood and adult intelligence, but not with adult psychiatric, neurological, or personality-related phenotypes.

Conclusions: The results of this study indicate that the biological processes underlying early-life head circumference overlap largely with those of adult head circumference. The associations of early-life head circumference with cognitive outcomes across the life course are partly explained by genetics.

Keywords: Head circumference, Genome-wide association study, Genetic correlations, Infancy

Background

Head circumference is a complex trait, commonly used as an indicator of brain volume during development and associated with child and adult intelligence [1–3]. It is also used as a measure of skeletal growth in fetal life, at birth and in early childhood [4, 5]. Twin studies show heritability estimates ranging from 75 to 90%, which are consistent across the life course [6]. Large genome-wide association studies (GWAS) have identified multiple

loci associated with child and adult head circumference, intracranial volume and brain volume [7–10]. Heritability estimates from GWAS range from 10 to 31% [8]. However, only two genetic loci associated with head circumference between 6 and 30 months have been identified so far [11]. Identifying additional genetic loci related to early-life head circumference may contribute towards our understanding of early brain development. This is important since observational studies have associated early brain development with several neurological and psychiatric diseases, such as Alzheimer's disease, schizophrenia and autism [12–17]. The underlying mechanisms are poorly understood. Both genetics and environmental factors play a role [18]. Additionally, the shared genetic contribution between early-life head circumference and later-life outcomes is yet unknown. Unravelling this shared genetic contribution may help us to better

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understand the etiology of later-life outcomes related to early-life head circumference.

We examined the genetic background of early-life head circumference by performing a two-stage GWAS meta-analysis comprising 25 studies with a combined sample size of 29,192 European-ancestry participants between 6 and 30 months of age. We also examined genetic correlations of early-life head circumference with anthropometrics, brain volume-related, neurological, psychiatric, cognitive, and personality related traits.

Methods

Study design

We conducted a two-stage meta-analysis in children of European ancestry to identify genetic loci associated with birth and early-life head circumference. Sex- and age-adjusted standard deviation scores (SDS) were created for head circumference between 6 to 30 months (closest to 18 months, if multiple measurements were available) using Growth Analyzer 3.0 across all studies [19]. In the case of twin pairs and siblings, only one of each twin or sibling pair was included, either randomly or based on genotyping or imputation quality.

In the discovery stage, we performed a meta-analysis of early-life head circumference in 21 studies ($N = 22,279$), including the Amsterdam Born Children and their Development-Genetic Enrichment Study (ABCD, $N = 1018$), the Avon Longitudinal Study of Parents and Children (ALSPAC, $N = 3960$), Children's Hospital of Philadelphia (CHOP, $N = 856$), the Copenhagen Prospective Studies on Asthma in Childhood 2000 (COPSAC2000, $N = 325$) and 2010 (COPSAC2010, $N = 603$), the Danish National Birth Cohort- preterm birth study (DNBC-PTB, $N = 508$), the Generation R Study (GenerationR, $N = 2299$), the Danish National Birth Cohort—the Genetics of Overweight Young Adults offspring study (DNBC GOYA-offspring, $N = 230$), the INfancia y Medio Ambiente [Environment and Childhood] Project, with two subcohorts that were entered into the meta-analysis separately (INMA-Sabadell and Valencia subcohort and INMA Menorca subcohort, $N = 550$), the German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development & Influence of life-style factors on the development of the immune system and allergies in East and West Germany (GINIplus&LISA, $N = 1455$), the Leipzig Research Center for Civilization Diseases—Child study (LIFE-Child, $N = 1365$), the Norwegian Mother Child Cohort (MoBa, $N = 836$), the Northern Finland Birth Cohort 1966 (NFBC 1966, $N = 4603$), the Northern Finland Birth Cohort 1986 (NFBC 1986, $N = 826$), the Physical Activity and Nutrition in Children Study (PANIC, $N = 372$), the Raine Study (Raine Study, $N = 1373$), the

Småbørns Kost Og Trivsel study, including two subcohorts (SKOT 1, $N = 170$ and SKOT 2, $N = 98$), the Special Turku Coronary Risk factor Intervention Project (STRIP, $N = 505$), and the TEENs of Attica: Genes and Environment (TEENAGE, $N = 327$).

In the replication stage of early-life head circumference analysis, we included 4 studies ($N = 6913$): 319 additional children from the INfancia y Medio Ambiente [Environment and Childhood] (INMA) Project (INMA-Gipuzkoa subcohort), 5644 additional children from the Norwegian Mother and Child Cohort (MoBa), the European Childhood Obesity Project (CHOP Study, $N = 366$), and the Exeter Family Study of Childhood Health (EFSOCH, $N = 584$). Characteristics of discovery and replication studies can be found in Additional file 2: Table S1. The study design of birth head circumference can be found in the Additional file 1.

Study-level analyses

Genome-wide association analyses were first run in all discovery cohorts for birth and early-life head circumference separately. Studies used high-density Illumina or Affymetrix Single Nucleotide Polymorphism (SNP) arrays, followed by imputation to the 1000 Genomes Project or Haplotype Reference Consortium (HRC). Before imputation, studies applied study specific quality filters on sample and SNP call rate, minor allele frequency and Hardy–Weinberg disequilibrium (see Additional file 2: Table S1 for details). Linear regression models assuming an additive genetic model were run in each study, to assess the association of each SNP with SDS head circumference, adjusting for principal components if this was deemed needed in the individual studies. As SDS head circumference is age and sex specific, no further adjustments were made. Before the meta-analysis, we applied quality filters to each study, filtering out SNPs with a minor allele frequency (MAF) below 1% and SNPs with poor imputation quality ($MACH\ r2_hat \leq 0.3$, $IMPUTE\ proper_info \leq 0.4$ or $info \leq 0.4$).

Meta-analysis

We performed fixed-effects inverse-variance weighted meta-analysis of all discovery samples using Metal [20]. Genomic control was applied to every study before the meta-analysis. Individual study lambdas before genomic control ranged from 0.99 to 1.03 (Additional file 2: Table S1). The lambda of the discovery meta-analysis was 1.02. Linkage Disequilibrium (LD) score regression analysis showed an intercept of 1.0, indicating that the slight inflation was mainly caused by polygenicity of early-life head circumference and not by population stratification, cryptic relatedness or other confounders [21, 22]. After the meta-analysis, we excluded SNPs for which

information was available in less than 50% of the studies or in less than 50% of the total sample size.

Genome-wide Complex Trait Analysis (GCTA) was used to select the independent SNPs for each locus [23]. We performed conditional analyses based on summary-level statistics and LD estimation between SNPs from the Generation R Study as a reference sample to select independently associated SNPs on the basis of conditional P values [23]. For early-life head circumference, 27 genome-wide significant or suggestive loci (P values $< 5 \times 10^{-8}$ and P values $< 5 \times 10^{-6}$, respectively) were taken forward for replication in the 4 replication cohorts. Fixed-effects inverse variance weighted meta-analysis was performed for these 27 SNPs combining the discovery samples and all replication samples, giving a combined analysis beta, standard error and P value (Table 1). SNPs that reached genome-wide significance (P value $< 5 \times 10^{-8}$) in the combined analysis were considered to be significantly associated with SDS-head circumference. For birth head circumference, SNPs were taken forward for replication, using the same methodology.

Functional mapping and annotation of genetic associations (FUMA)

To obtain predicted functional consequences for the SNPs that reached genome-wide significance in the combined meta-analysis, we used SNP2FUNC in FUMA, a web-based platform to facilitate and visualize functional annotation of GWAS results [24]. To annotate the nearest genes of the seven SNPs in biological context, we used the GENE2FUNC option in FUMA, which provides hypergeometric tests of enrichment of the list of nearest genes in 53 GTEx tissue-specific gene expression sets [24, 25]. We used GENE2FUNC for two sets of genes: 1. Nearest genes of seven SNPs; 2. Genes located in a region of 500 kb to either side of the 7 SNPs [24].

Colocalization analysis

We used Bayesian colocalization analysis to examine evidence for colocalization between early-life head circumference and eQTL signals (GTEx v7). Colocalization analyses were conducted using the R package *coloc*, <https://cran.r-project.org/web/packages/coloc>, as described previously [26]. Briefly, in each of the GTEx v7 tissues, all cis-eQTLs at FDR $< 5\%$ were identified. For each eQTL, GWAS summary statistics were extracted for all SNPs that were present in $> 50\%$ of the studies and $> 50\%$ of the total sample size and that were in common to both GWAS and eQTL studies, within 1 MB of the transcription start site of the gene. For each such locus, colocalization analyses were done with default parameters, testing the following hypotheses [26]:

- H_0 : No association with either trait;
- H_1 : Association with early-life head circumference only;
- H_2 : Association with gene expression only;
- H_3 : Association with early-life head circumference and gene expression, two distinct causal variants;
- H_4 : Association with early-life head circumference and gene expression, one shared causal variant.

Support for each hypothesis was quantified in terms of posterior probabilities, defined at SNP level and indicated by PP_0 , PP_1 , PP_2 , PP_3 or PP_4 , corresponding to the five hypotheses and measuring how likely these hypotheses are. In most pairs, no evidence for association was found with either trait. In case association was observed, it was mostly with a single trait. To define colocalization we used restriction to pairs of early-life head circumference and eQTL signals with a high posterior probability for colocalization, indicated by a $PP_4/(PP_3 + PP_4) > 0.9$.

The Database for Annotation, Visualization and Integrated Discovery (DAVID)

To explore biological processes, we used DAVID, with the seven nearest genes as input, using the Kyoto Encyclopedia of Genes and Genomes (KEGG) database [27, 28].

Linkage-disequilibrium score regression

The use of LD score regression to estimate genetic correlations between two phenotypes has been described in detail previously [29]. Briefly, LD score is a measure of how much a genetic variation is tagged by each variant. A high LD score indicates that a variant is in high LD with many nearby polymorphisms. Variants with high LD scores are more likely to contain true signals and have a higher chance of overlap with genuine signals between GWAS. To estimate LD scores, summary statistics from GWAS meta-analysis are used to calculate the cross-product of test statistics of per SNP, which is regressed on the LD score. The slope of the regression is a function of the genetic covariance between traits [29]:

$$E(z_{1j}z_{2j}) = \frac{\sqrt{N_1N_2}\rho_g}{M}l_j + \frac{\rho N_s}{\sqrt{N_1N_2}}$$

where N_i is the sample size of study i , ρ_g is the genetic covariance, M is the number of SNPs in the reference panel with a MAF between 5 and 50%, l_j is the LD score for SNP j , N_s quantifies the number of individuals that overlap both studies, and ρ is the phenotypic correlation amongst the N_s of overlapping samples. A sample overlap or cryptic relatedness between samples only affects the intercept from the regression but not the slope. Thus, estimates are robust even in presence of sample overlap

Table 1 Results of the 27 SNPs with P values $< 5 \times 10^{-6}$ in the discovery phase

SNP	CHR	Position	Nearest gene	EA/non_EA	P value discovery	P value replication	EAF _a	Beta (SE) combined	P value combined	Heterogeneity I ² combined analysis
rs8756 _{b,c,d}	12	66,359,752	HMG42	C/A	5.18×10^{-12}	4.62×10^{-3}	0.50	0.065 (0.009)	1.84×10^{-13}	0
rs9795522 _b	12	123,730,935	C12orf65	C/A	3.20×10^{-9}	3.86×10^{-5}	0.23	0.072 (0.010)	7.37×10^{-12}	0
rs10883848 _d	10	104,973,061	NT5C2	A/G	3.06×10^{-6}	0.03	0.35	0.058 (0.010)	9.99×10^{-10}	54.8
rs6095360	20	47,532,536	ARFGF2	G/A	3.53×10^{-8}	6.19×10^{-4}	0.32	0.055 (0.009)	4.39×10^{-9}	36.6
rs3134614	1	40,363,054	MYCL1	C/G	4.31×10^{-6}	7.75×10^{-4}	0.88	0.075 (0.013)	1.43×10^{-8}	0
rs6016511	20	39,709,255	TOP1	T/C	4.55×10^{-7}	0.02	0.68	0.052 (0.010)	4.02×10^{-8}	0
rs7792211 _d	7	50,707,141	GRB10	G/A	7.62×10^{-7}	0.01	0.42	0.051 (0.009)	4.43×10^{-8}	11.3
rs1490384 _{c,d}	6	126,851,160	CENPW	T/C	5.46×10^{-8}	0.14	0.51	0.049 (0.009)	5.70×10^{-8}	43.9
rs116536930	17	43,855,156	CRHR1	G/T	4.19×10^{-8}	0.53	0.51	0.055 (0.011)	2.27×10^{-7}	40.1
rs72952297	2	180,379,814	ZNF385B	T/G	2.07×10^{-6}	0.11	0.93	0.087 (0.018)	9.19×10^{-7}	0
rs12350281	9	20,637,773	MLL3	G/A	4.22×10^{-6}	0.03	0.05	0.152 (0.031)	9.98×10^{-7}	43.1
rs7658192	4	140,023,559	ELF2	T/G	2.29×10^{-7}	0.46	0.33	0.046 (0.010)	1.70×10^{-6}	62.9
rs143094271 _e	17	7,463,102	TNFSF12-TNFSF13	A/G	5.96×10^{-7}	0.44	0.02	0.133 (0.028)	2.02×10^{-6}	33.7
rs1014098	1	119,458,215	TBX15	C/T	2.67×10^{-6}	0.17	0.79	0.051 (0.011)	2.05×10^{-6}	30.3
rs77690628	8	26,189,223	PPP2R2A	A/T	1.02×10^{-6}	0.31	0.07	0.080 (0.017)	3.26×10^{-6}	24.6
rs9853018	3	141,101,961	ZBTB38	T/C	5.41×10^{-7}	0.62	0.45	0.040 (0.009)	5.30×10^{-6}	38.4
rs4674101	2	217,487,622	RPL37A	A/G	8.66×10^{-7}	0.57	0.31	0.043 (0.010)	6.56×10^{-6}	65.3
rs150266910	1	23,442,265	LUZP1	C/T	1.42×10^{-6}	0.65	0.83	0.052 (0.012)	1.04×10^{-5}	58.2
rs13067734	3	141,963,015	GK5	A/C	2.83×10^{-6}	0.55	0.52	0.037 (0.009)	1.22×10^{-5}	26.5
rs17223831	14	90,601,920	KCNK13	A/G	1.24×10^{-6}	0.18	0.14	0.067 (0.015)	1.30×10^{-5}	67.6
rs62580922	9	125,631,594	RC3H2	C/T	1.13×10^{-8}	0.35	0.07	0.072 (0.017)	1.52×10^{-5}	77.8
rs2448415	1	93,469,310	FAM69A	A/G	1.97×10^{-6}	0.81	0.47	0.037 (0.009)	2.56×10^{-5}	60.7
rs261752	5	39,328,506	C9	A/G	1.39×10^{-6}	0.70	0.55	0.035 (0.009)	7.63×10^{-5}	63.7
rs72979897	6	140,881,181	MIR3668	T/A	4.13×10^{-6}	0.88	0.04	0.100 (0.025)	8.26×10^{-5}	50.6
rs503783	6	161,959,649	PARK2	T/C	2.98×10^{-6}	0.66	0.27	0.037 (0.010)	1.59×10^{-4}	74.3
rs1113397574	5	31,968,320	PDZD2	T/C	4.56×10^{-6}	0.61	0.02	0.118 (0.032)	2.40×10^{-4}	58.5
rs77535478	9	77,533,287	TRPM6	A/G	1.28×10^{-6}	0.39	0.04	0.081 (0.026)	2.05×10^{-3}	75.4

Bolded P values indicate genome-wide significance in the combined analysis

CHR chromosome, **EA** effect allele, **EAF** effect allele frequency, **SE** standard error

*Genome-wide suggestive loci

^a From combined analysis

^b Locus previously reported for infant head circumference [11]

^c Locus previously reported for adult intracranial volume [7, 9]

^d Locus previously reported for adult head brain volume [8]

^e Locus previously reported for childhood and adult head circumference and intracranial volume [10]

when comparing traits across distinct GWAS populations. Estimates of genetic covariance are therefore not biased by overlapping samples. Similarly, in case of population stratification, the intercept is affected but it has only minimal impact on the slope since population stratification does not correlate with LD between variants.

Because of the correlation between the imputation quality and LD score, imputation quality is a confounder for LD score regression. Therefore, SNPs were excluded according to the following criteria: $MAF < 0.01$ or $INFO \leq 0.9$. The filtered GWAS results were uploaded on the online webtool, a web service with many GWAS meta-analyses available on which LD score regression has been implemented by the developers of the LD score regression method. In case multiple GWAS meta-analyses were available for the same phenotype, the genetic correlation with early-life head circumference was estimated using the most recent meta-analysis. Genetic correlations are shown in Fig. 3 and Additional file 1: Table S7.

Genetic risk score and percentage of variance explained

We combined the seven genome-wide significant SNPs from the combined meta-analysis into a Genetic Risk Score (GRS) by summing up the number of alleles that increase the SDS head circumference, weighted by the effect sizes from the combined meta-analysis. The GRS was rescaled to a range from 0 to 14, which is the maximum number of head circumference SDS increasing

alleles and rounded to the nearest integer. Linear regression analysis was used to examine the associations of the risk score with head circumference and intracranial volume at different ages. For these analyses data from the Generation R Study and UK Biobank were used. When calculating the risk score for the Generation R study, effect estimates from the combined meta-analysis were used after excluding Generation R from the meta-analysis. The variance explained was estimated by the adjusted R^2 of the models.

Results

Identification of genetic loci associated with early-life head circumference

Individual study characteristics are shown in Additional file 2: Table S1. In the discovery stage, we performed a fixed-effects inverse variance-weighted meta-analysis including data imputed to the 1000 Genomes or the Haplotype Reference Consortium (HRC) reference panels from 21 studies ($N = 22,279$). Using data from the discovery cohorts, single nucleotide polymorphisms (SNPs) at five independent loci reached genome-wide significance (P values $< 5 \times 10^{-8}$) and SNPs at another 22 loci showed suggestive associations with early-life head circumference ($5 \times 10^{-8} < P$ values $< 5 \times 10^{-6}$). A Manhattan plot of the discovery meta-analysis is shown in Fig. 1. No evidence of inflation by population stratification or cryptic relatedness was found (genomic inflation factor (λ) = 1.02 and LD-score regression intercept = 1.0) (Additional

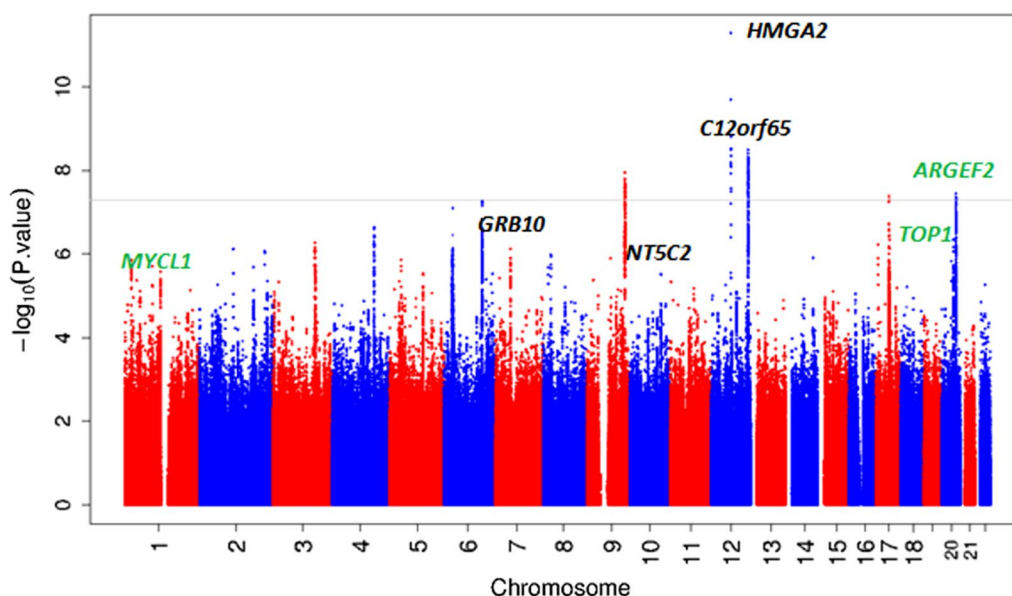


Fig. 1 Manhattan plot of results of the discovery meta-analysis of 21 GWAS. On the x-axis the chromosomes are shown. On the y-axis the $-\log_{10}$ of the P value is shown. Novel SNPs are shown in green. Known SNPs are shown in black. The genome wide significance cutoff of 5×10^{-8} is represented by the grey dotted line

file 1: Fig. S1) [21]. The index SNPs from each of the 27 genome-wide and suggestive loci were followed up in four replication cohorts ($N=6913$). The results of the discovery, replication and combined analyses are shown in Table 1 and Additional file 1: Tables S2 and S3. Results of the discovery analysis for SNPs with P values $< 5 \times 10^{-6}$ are shown in Additional file 3: Table S4.

Of the 27 SNPs identified in the discovery meta-analysis, seven reached genome-wide significance in the combined meta-analysis, in which we used data from the discovery and replication stage. An identified locus was defined to be a known locus if the index SNP was within a range of 500 kb upstream to 500 kb downstream of and in LD ($r^2 \geq 0.2$) with a previously reported SNP for head circumference, intracranial volume, or brain volume at any age [7–11]. Of the seven genome-wide significant SNPs, three were novel: rs6095360 near *ARFGEF2*, rs3134614 near *MYCL1*, and rs6016511 near *TOPI* (Table 1 and Additional file 1: Tables S2 and S3). Regional plots of these three loci are shown in Fig. 2. The remaining four SNPs mapped to loci previously identified from GWAS on infant head circumference, adult intracranial volume, and/or adult brain volume (nearest genes: *HMG2A*, *C12orf65*, *NT5C2*, and *GRB10*) [7, 10, 11].

Six SNPs located within 500 kb (upstream or downstream) from rs6095360 (*ARFGEF2*), rs3134614 (*MYCL1*), and rs6016511 (*TOPI*) have been previously reported in relation to adult height [30]. The linkage disequilibrium (LD) of the three novel SNPs near *ARFGEF2*, *MYCL1*, and *TOPI* with these six adult height SNPs was weak to moderate. We found suggestive evidence of association for rs6095360 (*ARFGEF2*) with early-life length in 28,949 participants between 6 and 30 months of age in an unpublished GWAS meta-analysis of 24 cohorts (P value 4.58×10^{-7}), but the other two novel SNPs did not show evidence of association (Additional file 1: Table S5).

We also performed a meta-analysis of birth head circumference in a total of 32,084 participants. None of the SNPs reached genome-wide significance in this analysis. A total of 11 SNPs with P values between 5×10^{-8} and 5×10^{-6} were taken forward for replication ($N=3750$) and combined analyses, but none were genome-wide significant in the combined analysis. Therefore, no follow-up analyses were performed for birth head circumference. A Manhattan plot and a Quantile–Quantile plot of the discovery meta-analysis of birth head circumference are

shown in Additional file 1: Figs. S2 and S3. Results of the discovery analysis for SNPs with P values $< 5 \times 10^{-6}$ are shown in Additional file 4: Table S6.

Functional characterization

To gain insight into the function of the seven SNPs associated with early-life head circumference, we used several strategies. First, using Bayesian colocalization analysis, we examined evidence of colocalization between GWAS and eQTL signals for the seven index SNPs (GTEx v7), but did not find a signal at any of the seven loci. Second, to explore biological processes, we used the Kyoto Encyclopedia of Genes and Genomes (KEGG) database in the Database for Annotation, Visualization and Integrated Discovery (DAVID) with the seven SNPs and their nearest genes as input [27, 28], but no enriched biological processes were identified. Third, we did a look-up of the seven nearest genes in mouse-knockout data but there was no phenotypic information available for any of these gene knockouts [31]. Fourth, we examined gene expression profiles for the nearest genes to the seven SNPs with GTEx v7 in 53 tissues, using the tool for Functional Mapping and Annotation of Genome-Wide Association Studies (FUMA) [24, 25]. We did not find significant differential expression for these seven nearest genes. Going a step further, we included all genes within a range of 500 kb upstream to 500 kb downstream of the seven index SNPs and found significant differential expression in several brain structures, including the putamen, amygdala, hippocampus, caudate, nucleus accumbens, substantia nigra, and anterior cingulate cortex, and in other tissues such as the heart, pancreas and liver [25].

Shared genetic background of early-life head circumference with childhood and adult outcomes

First, to examine whether associations between early-life head circumference and phenotypes in later life from observational studies were at least partly genetically explained, we estimated genetic correlations between early-life head circumference and other traits, using LD score regression, which is based on the genome-wide meta-analysis results [29]. We found positive genetic correlation coefficients for early-life head circumference with birth length ($R_g = 0.57$, P value $= 3.61 \times 10^{-12}$), birth weight ($R_g = 0.48$, P value $= 2.51 \times 10^{-8}$), adult height ($R_g = 0.34$, P value $= 9.77 \times 10^{-11}$), adult body mass index

(See figure on next page.)

Fig. 2 a–c Locus zoom plots of the 3 novel loci. Shown are the results of the meta-analysis. Regional association plot of the 3 novel loci. SNPs are plotted with their P values from the discovery stage (as $-\log_{10}$; left y-axis) as a function of genomic position (x-axis). Estimated recombination rates (right y-axis) taken from 1000 Genomes, March 2012 release are plotted to reflect the local LD-structure around the top associated SNP (indicated with purple color) and the correlated proxies (indicated in colors)

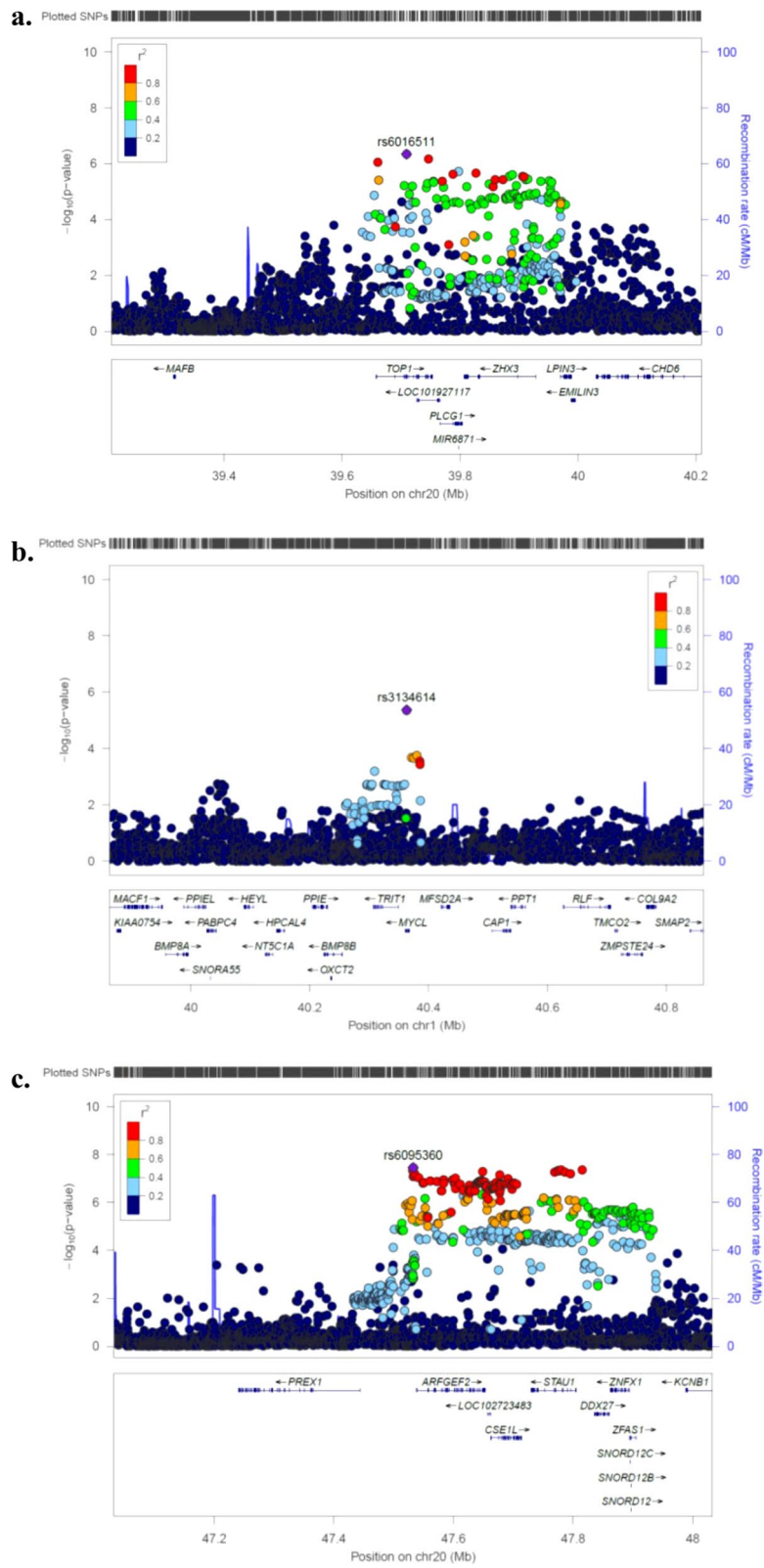


Fig. 2 (See legend on previous page.)

(BMI) ($R_g=0.13$, P value=0.03), adult intracranial volume ($R_g=0.71$, P value= 1.44×10^{-5}) and several cognitive outcomes, including childhood intelligence (age range 6–18 years) ($R_g=0.27$, P value=0.04), years of schooling ($R_g=0.18$, P value= 6.0×10^{-4}), and adult intelligence ($R_g=0.25$, P value= 1.0×10^{-4}), (Fig. 3 and Additional file 1: Table S7). We did not find genetic correlations with any psychiatric (for instance bipolar disorder and autism spectrum disorder), neurological (Parkinson's disease, Alzheimer's disease) or personality-related outcomes (for instance neuroticism) (P values > 0.05) (Additional file 1: Table S7).

Second, we performed a look-up of the seven identified SNPs in GWAS meta-analyses data on potentially related phenotypes, including adult intracranial volume, intelligence, Alzheimer's disease, neuroticism, depression and educational attainment [7, 32–35]. Rs10883848 (*NT5C2*) was genome-wide significantly associated with adult intracranial volume (P value= 1.48×10^{-9}). All effect estimates for intracranial volume were in the same direction as those for head circumference in early-life

(Additional file 1: Table S8). Additionally, rs6095360 (*ARFGF2*) was associated with adult intelligence at a genome-wide level (P value= 2.31×10^{-16}). We did not observe evidence of genome-wide significant associations with Alzheimer's disease, neuroticism, depression or educational attainment. Suggestive evidence for association was observed for rs8756 (*HMGA2*) with adult intracranial volume (P value= 6.32×10^{-8}), for rs9795522 (*C12orf65*) with adult intelligence (P value= 1.41×10^{-6}) and for rs8756 (*HMGA2*) with educational attainment (P value= 1.41×10^{-6}) (Additional file 1: Tables S9–13). None of the SNPs showed evidence of association with birth head circumference in the GWAS meta-analysis (Additional file 1: Table S14).

Third, we calculated a combined genetic risk score (GRS) using the seven index SNPs identified in the current study. We summed the number of head circumference-increasing alleles weighted by the effect sizes from the combined meta-analysis after excluding the Generation R Study, in which we tested the GRS longitudinally. The GRS was associated with fetal head circumference

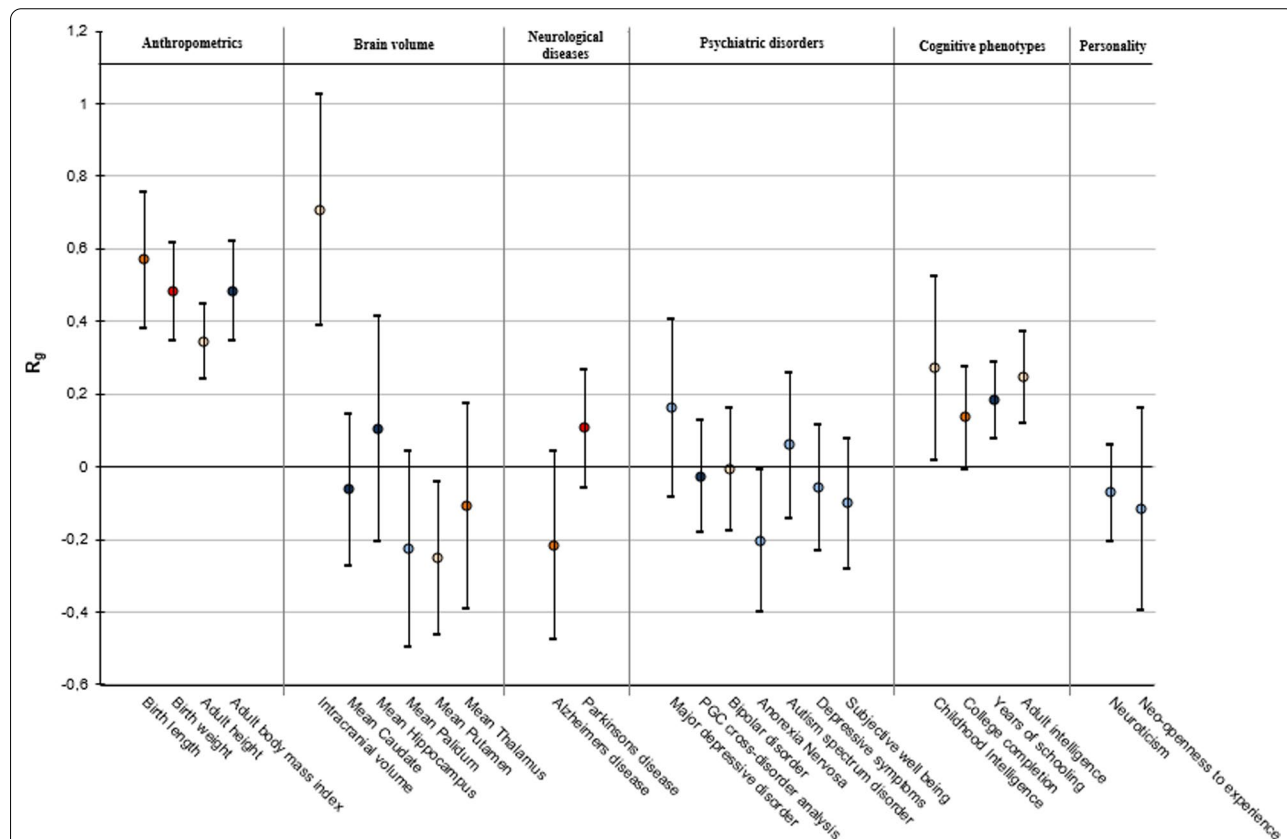


Fig. 3 Genome-wide genetic correlations between early-life head circumference and adult traits and diseases. On the x axis the traits and diseases are shown. The y-axis shows the genetic correlations (R_g) and corresponding standard errors, indicated by error bars, between early-life head circumference and each trait, estimated by LD score regression. The genetic correlation estimates (R_g) are colored according to their intensity and direction. Red indicates a positive correlation, blue indicates a negative correlation. References can be found in Additional file 1: Table S7

in the third trimester of pregnancy (N=1984), at post-natal ages 1 month (N=1501), 6 months (N=1662), 11 months (N=1528), and 6 years (N=4010) and at the mean (SD) age of 64 (7.5) years (N=22,152) in UK Biobank data (*P* values < 0.05) (Fig. 4 and Additional file 1: Table S15).

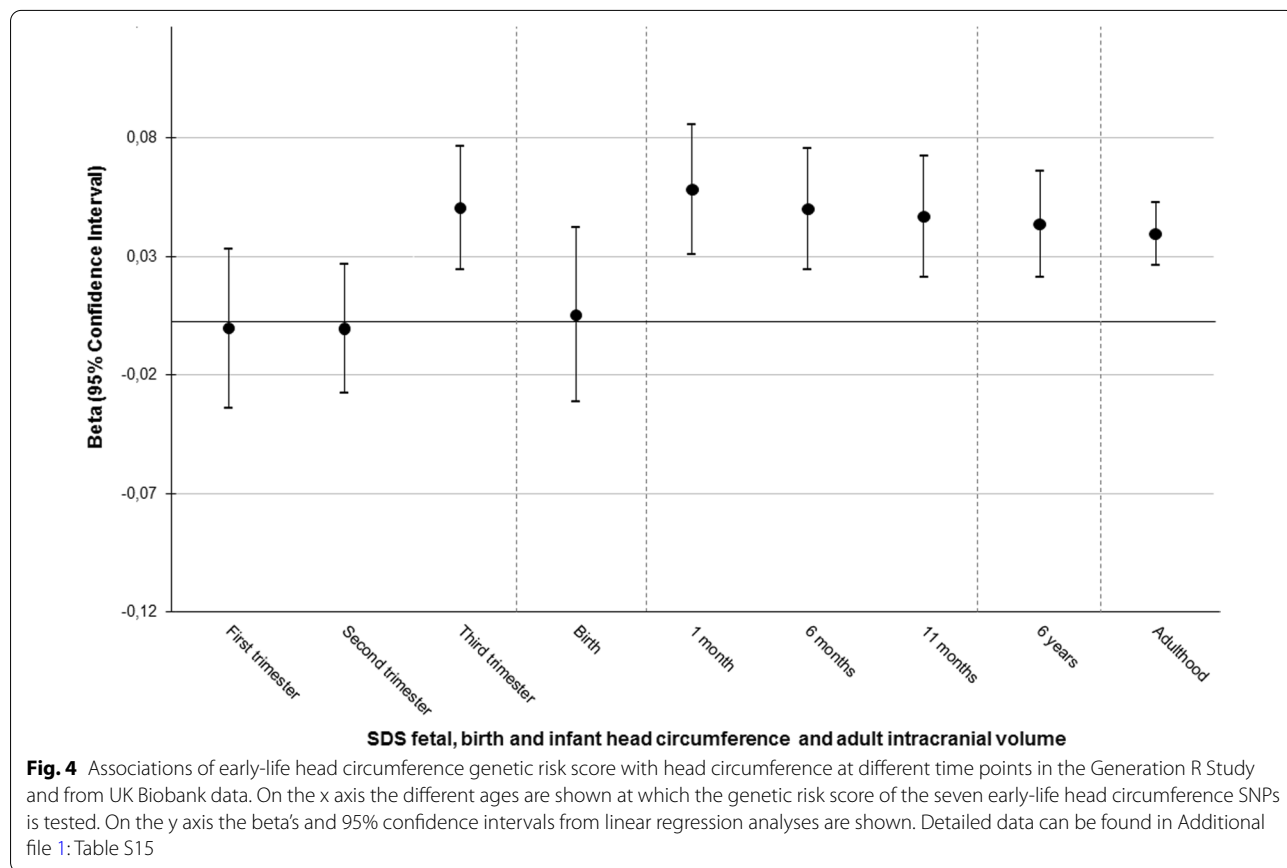
Discussion

In a GWAS meta-analysis including 29,192 participants of European ancestry aged 6 to 30 months of age, we identified seven genome-wide significant SNPs associated with early-life head circumference, of which three were novel and had not been related with head circumference, intracranial volume or brain volume before. We observed positive genetic correlations between early-life head circumference and adult intracranial volume as well as cognitive outcomes.

We used multiple approaches to identify potential underlying mechanisms. As there is no strong evidence linking the nearest genes to the seven SNPs as causal genes, we included all genes within 500 kb to either side of the genome-wide significant SNPs in a GTEx analysis. We found differential expression of these genes in different brain structures that are related to cognitive

functions and emotional control, indicating a potential functional role of these genes in the brain [36–39]. However, as donors aged 20–79 years were included in the GTEx data source, we were not able to look at expression of the genes in brain structures in early life. Using colocalization analysis, no potentially causal genes were identified [26]. Future studies should also determine whether the nearest genes, identified in this study, are indeed the causal genes and assess their expression in child brain structures.

The potential roles of the nearest genes to the novel loci are still poorly understood. *MYCL1*, (*MYCL* proto-oncogene, BHLH transcription factor), and *TOPI* (DNA topoisomerase 1) have been suggested to play a role in various types of cancer [40–44]. The role of these genes in the development of head circumference in early life is currently unknown. A mutation in *ARFGEF2* has been previously associated with several phenotypes related to brain development, including microcephaly [45, 46]. The three novel SNPs are located near regions that have been previously reported for adult height, indicating that they might represent loci involved in growth [30]. However, the strong association of rs6095360 (nearest gene: *ARFGEF2*) with adult intelligence (*P* value = 2.31×10^{-16})



might indicate a role in brain development as well [32]. Future functional studies should investigate the role of these genes and should determine whether these genes are indeed causal.

Observational studies suggest that early life head circumference is not only related to intracranial volume in adults, but also to adult intelligence, Alzheimer's disease, schizophrenia and autism [1–3, 12–17]. In observational studies of such associations, effect estimates may be influenced by confounding factors and reverse causation, potentially evoking spurious associations [47, 48]. Genetic studies such as ours can provide more insight into the etiology of complex diseases. We found a strong genetic correlation of head circumference in early life with intracranial volume in adults, underlining the idea that early-life head circumference is a valid measure for brain growth during early development [3, 7]. Abnormal growth trajectories of head circumference are related to adverse neurological outcomes [49]. Additionally, variation within the normal range of head circumference has been reported to be associated with cognitive and behavioral traits [2, 50, 51]. In the current study, we observed positive genetic correlations for head circumference in early life with childhood intelligence, years of schooling and adult intelligence. These findings indicate that the association of early-life head circumference with cognitive function from observational studies is at least partly explained by a shared genetic background, which is in line with the observed positive genetic correlations between intracranial volume and cognitive function in the literature [7, 8, 52]. Altogether, the findings from the current study and from previous literature suggest that the associations between measures of early-life brain volume and cognition decades later are partly genetically explained.

It has been suggested that heritability estimates are consistent from childhood onwards [6]. Whether this genetic stability starts from early life onwards, is currently not well studied. We observed evidence for association of two of the seven SNPs with adult intracranial volume [7]. We combined the seven index SNPs into a weighted GRS. Although we have used effect sizes of the meta-analysis after excluding the Generation R Study, the discovery of the seven SNPs was based on the meta-analysis including the Generation R Study, potentially resulting in overfitting of the GRS. We found an association of the GRS with fetal head circumference in third trimester, head circumference in infancy and childhood and intracranial volume in adulthood. The effect estimates were largely similar for the different time points. We did not observe an association of the GRS with birth head circumference. This may be explained by the larger variance in birth head circumference that might be present

due to the deformation of the head during birth. Also, in the GWAS meta-analysis of head circumference at birth, no SNPs were genome-wide significantly associated with birth head circumference. Thus, the genetic background of early-life head circumference seems to partially overlap with the genetic background of related measures in later life. The SNPs identified in infancy seem to represent effects across multiple ages. However, as not all SNPs identified for early-life head circumference were associated with adult intracranial volume, it has been suggested that some of the underlying mechanisms are age-specific.

Conclusions

We identified seven SNPs associated with early-life head circumference. Three of these are novel and four mapped to loci that are known for head circumference, intracranial volume, or brain volume. We observed a strong positive genetic correlation of early-life head circumference with adult intracranial volume and cognitive outcomes in childhood and adulthood. The well-known associations of head circumference with later cognitive phenotypes are partly explained by genetics. Our findings may contribute to the understanding of the early-life brain development, which may lay the foundation for diseases later in life.

Abbreviations

GWAS: Genome-wide association studies; SDS: Standard deviation scores; MAF: Minor allele frequency; KEGG: Kyoto Encyclopedia of Genes and Genomes; HRC: Haplotype Reference Consortium; SNPs: Single nucleotide polymorphisms; LD: Linkage disequilibrium; DAVID: Database for Annotation, Visualization and Integrated Discovery; FUMA: Functional Mapping and Annotation of Genome-Wide Association Studies; BMI: Body mass index; GRS: Genetic risk score.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12920-022-01281-1>.

Additional file 1. Additional data includes 15 tables, 3 figures and additional cohort information and methods.

Additional file 2. Characteristics of discovery and replication studies.

Additional file 3. Results of the discovery analysis for SNPs with P-values $< 5 \times 10^{-6}$.

Additional file 4. Results of the discovery analysis for SNPs with P-values $< 5 \times 10^{-6}$ for birth head circumference.

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Author contributions

SV, JFF and VVWJ designed the research and wrote the paper. SV, JFF and JPB analyzed the meta-analysis data. JFF and VVWJ were responsible for the study design of an individual contributing study. JFF, VVWJ and SFAG were responsible for the management of an individual contributing study. SV and SFAG were involved in sample collection and phenotyping of an individual contributing study. SFAG genotyped the data of an individual contributing study.

SV, JFF and JPB analyzed data of an individual contributing study. All authors provided comments and consultation regarding the analyses, interpretation of the results and manuscript. SV, JFF and VVWJ had primary responsibility for final content. All authors gave final approval of the version to be published. All authors read and approved the final manuscript.

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IOW

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Lifestyle—Immune System—Allergy Study and German Infant Study on the influence of Nutrition Intervention (LISA + GINI)

The GINIplus study was mainly supported for the first 3 years of the Federal Ministry for Education, Science, Research and Technology (interventional arm) and Helmholtz Zentrum Munich (former GSF) (observational arm). The 4 year, 6 year, 10 year and 15 year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum Munich (former GSF), Research Institute at Marien-Hospital Wesel, LMU Munich, TU Munich and from 6 years onwards also from IUF—Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf,

FKZ20462296). Further, the 15 year follow-up examination of the GINIplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project, and as well by the companies Mead Johnson and Nestlé. The LISA study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research—UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4 year, 6 year, 10 year and 15 year follow-up examinations of the LISA study were covered from the respective budgets of the involved partners (Helmholtz Zentrum Munich (former GSF), Helmholtz Centre for Environmental Research—UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF—Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15-year follow-up examination of the LISA study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project.

Norwegian Mother and Child (MoBa) Cohort Study (Pål R. Njølstad)

MOBA: The Norwegian Mother and Child Cohort Study was supported by grants from the European Research Council (AdG #293574), the Bergen Research Foundation ("Utilizing the Mother and Child Cohort and the Medical Birth Registry for Better Health"), Stiftelsen Kristian Gerhard Jebsen (Translational Medical Center), the University of Bergen, the Research Council of Norway (FRIPRO grant #240413), the Western Norway Regional Health Authority (Strategic Fund "Personalized Medicine for Children and Adults", and Open Grants «Understanding infant weight biology through genomics and deep phenotyping» grant #912250), and the Norwegian Diabetes Foundation; the Research Council of Norway through its Centres of Excellence funding scheme (#262700), Better Health by Harvesting Biobanks (#229624).

Norwegian Mother and Child (MoBa) Cohort Study (Bo Jacobsson)

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Northern Finnish Birth Cohort Study 1966 (NFBC66) and 1968 (NFBC86)

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The Physical Activity and Nutrition in Children (PANIC) Study

The PANIC Study has financially been supported by grants from Ministry of Education and Culture of Finland, Ministry of Social Affairs and Health of Finland, Research Committee of the Kuopio University Hospital Catchment Area (State Research Funding), Finnish Innovation Fund Sitra, Social Insurance Institution of Finland, Finnish Cultural Foundation, Foundation for Paediatric Research, Diabetes Research Foundation in Finland, Finnish Foundation for Cardiovascular Research, Juho Vainio Foundation, Paavo Nurmi Foundation, Yrjö Jahnnson Foundation, and the city of Kuopio. The PhD students and post-doctoral researchers of The PANIC Study have financially been supported by personal grants from Program for Clinical Research and Program for Health Sciences of Doctoral School of University of Eastern Finland, Finnish Doctoral Programs in Public Health, Finnish Doctoral Program in Oral Sciences, European Commission Marie Curie Fellowship Programme, North Savo Regional Fund of Finnish Cultural Foundation, Juho Vainio Foundation, Päiviikki and Sakari Sohlberg Foundation, Foundation for Paediatric Research, Diabetes Research Foundation in Finland, Finnish Foundation for Cardiovascular Research, Emil Aaltonen Foundation, Paulo Foundation, Jalmary and Rauha Ahokas Foundation, Aarne and Aili Turunen Foundation, Finnish Medical Foundation, Jenny and Antti Wihuri Foundation, Orion Foundation, Urho Känkänen Foundation, Finnish Association for the Study of Pain, Finnish Dental Society Apollonia, Northern Savo Dental Association, Health Centre Dentist Association, Finnish Female Dentists Association, Kuopio Naturalists' Society, Olvi Foundation, and the city of Kuopio.

Prevention and incidence of asthma and mite allergy birth cohort study—(PIAMA)

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Project Viva

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The Raine Study

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SKOT (1 & 2)

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TDCOB

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TEENS of Attica: Genes and Environment Study (TEENAGE)

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Availability of data and materials

GWAS summary data will be deposited at the EGG website (<https://egg-consortium.org/>) at publication. Individual study data are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All studies were approved by the national research ethics committee. Study-specific details are shown in the acknowledgements and supplemental cohort information. Informed consent to participate was obtained for all participants. Detailed and study-specific information can be found in the acknowledgements and supplemental cohort information.

Consent for publication

Not applicable.

Competing interests

MMcC: The views expressed in this article are those of the author(s) and not necessarily those of the NHS, the NIHR, or the Department of Health. He serves on advisory panels for Pfizer, NovoNordisk, Zoe Global; has received honoraria from Merck, Pfizer, NovoNordisk and Eli Lilly; has stock options in Zoe Global; has received research funding from Abbvie, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Merck, NovoNordisk, Pfizer, Roche, Sanofi Aventis, Servier & Takeda. Ms Receives funding from Pfizer Inc. for a project not related to this research. The other authors declare that they have no competing interests.

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