Population-based GWAS samples and phenotype measurements

The EArly Genetics and Lifecourse Epidemiology (EAGLE) Consortium is an international consortium of pregnancy and birth cohorts that aims to collaborate to investigate the genetic basis of phenotypes in antenatal and early life and childhood. EAGLE covers a broad range of pathways and phenotypes, integrating closely with the DOHaD (developmental origins of health and disease) community. Further details can be found here: http://research.lunenfeld.ca/eagle/. Descriptions for each cohort that participated in this study are detailed below. All participants provided written informed consent and studies were approved by local Research Ethics Committees and/or Institutional Review boards.

Individual Study Cohort Descriptions

*Amsterdam Born Children and their Development (**ABCD**)*

Study design

The Amsterdam Born Children and their Development (ABCD) cohort study is a large, community-based birth cohort, which started in 2003 with the inclusion of 8,000 pregnant women living in Amsterdam and its main aim is to study factors in early life (during pregnancy and infancy) that explain health later in life. Detailed information on life style habits, psychosocial determinants, obstetric complications, blood pressure course during pregnancy, as well as childhood growth patterns has been gathered.[1] Data for this study comes from ABCD-Genetic Enrichment (ABCD-GE) study, a sub-study of 1192 ethnic Dutch children. The blood was collected from a simple finger prick during the 5-year health check-up of the children (2008-2010). DNA was extracted from the dried blood spots.[2] Approval of the study was obtained from the Central Committee on Research Involving Human Subjects in The Netherlands, the medical

ethics review committees of the participating hospitals and the Registration Committee of the Municipality of Amsterdam and written consent was obtained from participating parents.

Sleep duration assessment

At age 7-8, child sleep and sleep problems were assessed using the Dutch Child Sleep Habit Questionnaire[3]. To assess sleep duration, mothers were asked on "Child's usual amount of sleep each day, combining night time sleep and naps (in hours)".

*Avon Longitudinal Study of Parents and Children (**ALSPAC**)*

Study design

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a prospective study, which recruited pregnant women with expected delivery dates between April 1991 and December 1992 from Bristol UK. The study methods are described elsewhere and on the study website (www.alspac.bris.ac.uk).[4] Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

Sleep duration assessment

Sleep duration in children was assessed by parental questionnaire according to the following open-ended question: "Normally during term-time what time in the evening does your child go to sleep? During term-time what time does she normally wake-up in the morning?" These questions were to be answered for school days and weekends separately. Sleep duration in school days was used in this study.

*Brain development and Air pollution ultrafine particles in school children (**BREATHE**)*

Study design

The BRain dEvelopment and Air polluTion ultrafine particles in scHool children (BREATHE) is a prospective cohort study that aims to analyze the association between air pollution and cognitive development of scholars.[5] DNA samples from 2,492 children were obtained from saliva and a final subset of 1,778 children was selected for genome-wide genotyping after applying a filtering criteria (low quality DNA, no neuropsychological data, non-Caucasian descent origin and not born in Spain, parents born in Europe, and adopted children). Genome-wide genotyping was performed at the Spanish National Genotyping Centre (CEGEN) coordinated by the Spanish National Cancer Research Centre (CNIO). All parents and legal guardians signed the informed consent approved by the Ethical Committee of the IMIM-ParcSalut Mar.

Sleep duration assessment

Child sleep duration was assessed by parental questionnaire according to the following open-ended question: "How long does your child sleep during weekdays?"

*Generation R Study (**GEN-R**)*

Study design

The Generation R Study is a population-based prospective cohort study. All children were born between April 2002 and January 2006. This study is designed to identify early environmental and genetic determinants predictors of growth, development, and health from foetal life until young adulthood and has been described previously in detail.[6] DNA was extracted from cord blood taken at birth. Children of Northern European descent, as determined by principal

component analyses of genome wide association (GWA) data, were selected. The details of DNA extraction, genotyping, imputation, and quality control have been previously described.[7] Of 5,908 children with DNA available, 1,979 children of Northern European descent (52% boys) had SNP data and available data on sleep duration. The Medical Ethical Committee of the Erasmus Medical Centre, Rotterdam has approved the study protocol, and participants have given informed consent in writing.

Sleep duration assessment

Sleep duration in children was assessed by parental questionnaire at 24 months. Average sleep duration of children per 24 hours was estimated by the number of sleeping hours during both day and night. Detailed information on phenotype are published elsewhere.[8]

*Glycyrrhizin in Licorice (**GLAKU**)*

Study design

Glaku is an urban community-based cohort comprising 1049 healthy, singleton infants born between March and November 1998 in Helsinki, Finland. In 2009–2011, all initial cohort members who had given permission to be contacted and whose addresses were traceable (*N*=920, 87.7% of the original cohort in 1998) were invited to a follow-up; 692 (75.2%) mothers of the adolescent invitees could be contacted by phone. Of them, 451 (65.2% of those who could be contacted by phone, 49% of the invited) participated in a follow-up at a mean age of 12.3 years (*SD*=0.5, range 11.0–13.2 years) and 393 gave saliva and 211 blood for genetic analyses. In 277 participants DNA was extracted from saliva and in 80 participants from leukocytes. After quality control procedures 352 samples remained for the analyses. Data on sleep duration at an average age of 11.9 (*SD*=1.3) were available in 321 (*n*=165, 51.4% girls) of those genotyped

successfully. Detailed information on the selection of the Glaku participants and on the study design can be found elsewhere.[9-11] Ethics Committees of the City of Helsinki Health Department and Children's Hospital in Helsinki University Central Hospital approved the study protocol. Written informed consent was obtained from parent/guardian and child.

Sleep duration assessment

Sleep duration was parent-reported and calculated as the arithmetic difference from answers to questions "What time does your child go to sleep on schooldays?" (before 19.00/ 19.30/ 20.00/ 20.30/ 21.00/ 21.30/ 22.00/ 22.30/ 23.00/ 23.30/ 24.00/ 00.30/ 01.00/ 01.30/ 02.00 or later) and "What time does your child wake up on school mornings?" (before 05.00/ 05.30/ 06.00/ 06.30/ 07.00/ 07.30/ 08.00 or later).

*Lifestyle-Immune System- Allergy Study and German Infant Study on the Influence of Nutrition Intervention (**LISA+GINI**)*

Study design

The "influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany PLUS the influence of traffic emissions and genetics" (LISAplus) Study is a population based birth cohort study. A total of 3,097 healthy, mature (gestational age over 37 weeks) neonates with a birth weight over 2500g were recruited between 1997 and 1999 in Munich, Leipzig, Wesel and Bad Honnef. A total of 5,991 mothers and their newborns were recruited into the German Infant study on the influence of Nutrition Intervention (GINI) between September 1995 and June 1998 in Munich and Wesel. Detailed descriptions of the LISA and GINI studies have been published elsewhere.[12, 13] For both studies, approval by the local Ethics Committees and written consent from participant's families were obtained.

Sleep duration assessment

Child sleep duration was assessed by parental questionnaire according to the following open-ended question: “How many hours does your child sleep on average: In total, number hours per day and night.”

*Infancia y media ambiente project (**INMA**)*

Study design

The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project is a network of birth cohorts in Spain that aim to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development.[14] Data for this study comes from INMA Sabadell, INMA Valencia and INMA Menorca. DNA was obtained from cord blood, whole blood or saliva collected at 4years using the Chemagen protocol at the Spanish National Genotyping Centre (CEGEN). Children whose parents reported to be white and to be born in Spain or in European countries and that were not lost during the follow-up were selected for genotyping. The study has been approved by Ethical Committee of each participating centre and written consent was obtained from participating parents.

Sleep duration assessment

Child sleep and sleep-related habits were assessed by parental questionnaires. To assess sleep duration, parents were asked to reply to the following open-ended question: “How long does the child sleep per day, including naps (in hours)?”.

Table S1: Information on genotyping methods, quality control, imputation and statistical analysis of studies included in GWAS meta-analysis of sleep duration in children

	Genotyping and QC							Imputation and analysis		Meta-level QC				
Cohort	Platform	Caling algorithm	MAF (%)	SNP call rate (%)	P for HWE	Sample call rate (%)*	Final N SNPs	Imputation	Analysis software	Initial N SNPs	Final N SNPs**	% filtered	lambda	N
ABCD	Illumina HumanCoreBeadChip	Genome Studio	>1	>95	>10e-6	>97	277,644	IMPUTE2[15]	SNPTEST[16]	-	-	-	-	929
ALSPAC	Illumina 550K	GenCall	>1	>97	>10e-7	>97	488,325	MACH[17]		30,061,895	8,320,472	27.68%	1.01	5434
BREATHE	Illumina HumanCoreBeadChip	GeneTrain2.0	>1	>95	>10e-6	>97	240,103	IMPUTE2	SNPTEST	37,721,381	6,885,016	18.25%	1.00	1593
GEN-R	Illumina Human 610K & 660W	Genome Studio	≥0.1	>97.5	>10e-7	>97.5	518,245	MACH	GRIMP[18]	30,072,738	6,890,910	22.91%	1.00	1979
GLAKU	Illumina Human Omni Express Exome 1.2 bead chip	-	>0	>99	>0.005	-		IMPUTE2	SNPTEST	-	-	-	-	321
INMA	Illumina HumanOmni1-Quad Beadchip	GeneTrain2.0	>1	>95	>10e-6	>98	817,131	IMPUTE	SNPTEST	38,040,556	6,275,820	16.50%	1.00	940
LISA+GINI	Affymetrix Genome-Wide Human SNO Arrays 5.0 and 6.0	BRLMM-P (5.0) BIRSEEDv2-(6.0)	>1	>95	>10e-5	>95	351,488 (5.0) 718,039 (6.0)	IMPUTE	SNPTEST	13,486,809	5,306,521	39.35%	1.00	608

*In addition samples were checked for excess of heterozygosity, sex discordances, relatedness and population stratification

**filtered by MAF>1% EMAC (expected allele count)>100, imputation quality R2>0.3 or INFO>0.4

Figure S1. P-Z plots (x-axis: reported p values on –log10 scale, y-axis: p-values calculated from the Z-statistics on –log10 scale, using the reported beta estimates and standard errors)for each study participating in the GWAS meta-analysis of sleep duration in children (*N*=10,554). No major analytical issues with beta's, standard errors and p-values were identified (concordance with the identity line)

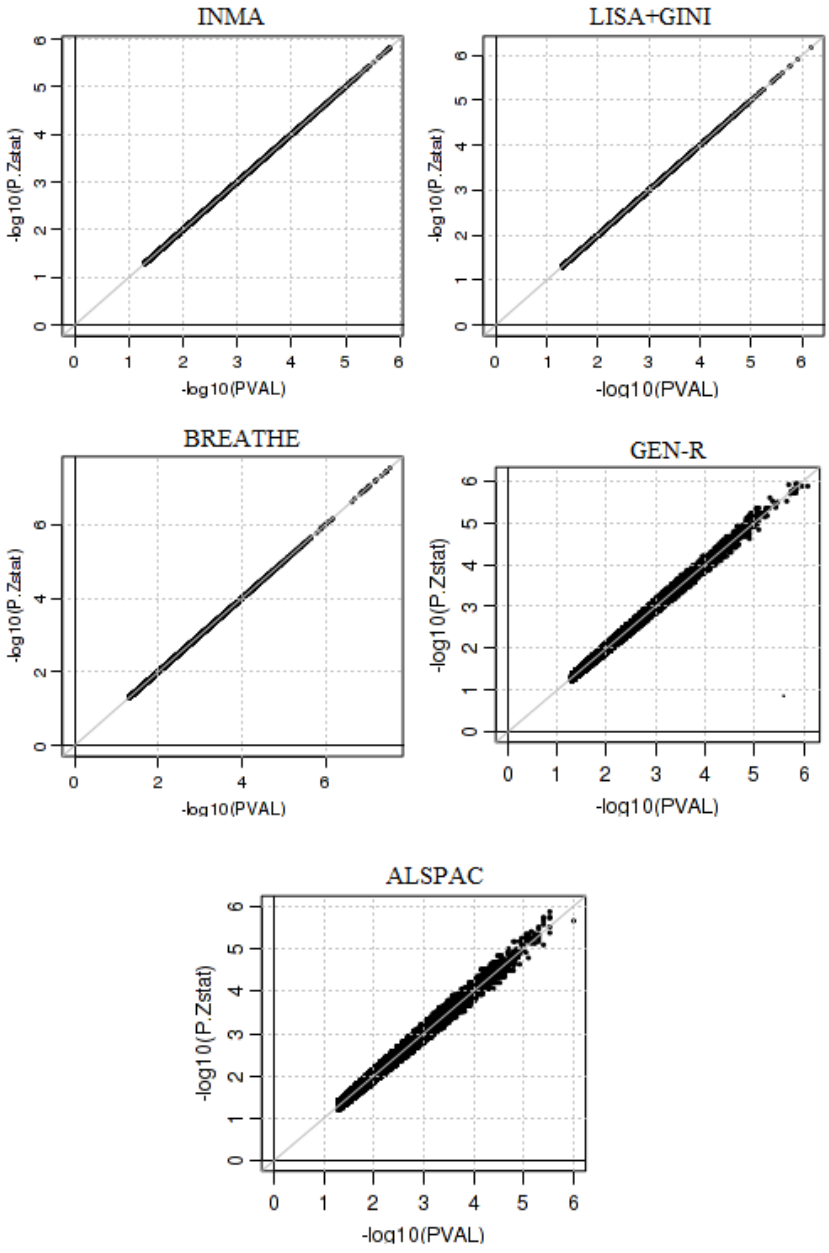

Figure S2. Effect allele frequency (EAF) plot reporting study specific allele frequencies against allele frequencies expected from 1000 Genome (EUR), for studies participating in the GWAS meta-analysis of sleep duration in children (*N*=10,554). SNPs with deviating allele frequencies (red dots) were excluded from further analyses. They are mainly variants named MERGED in the 1000G as well as array specific variants.

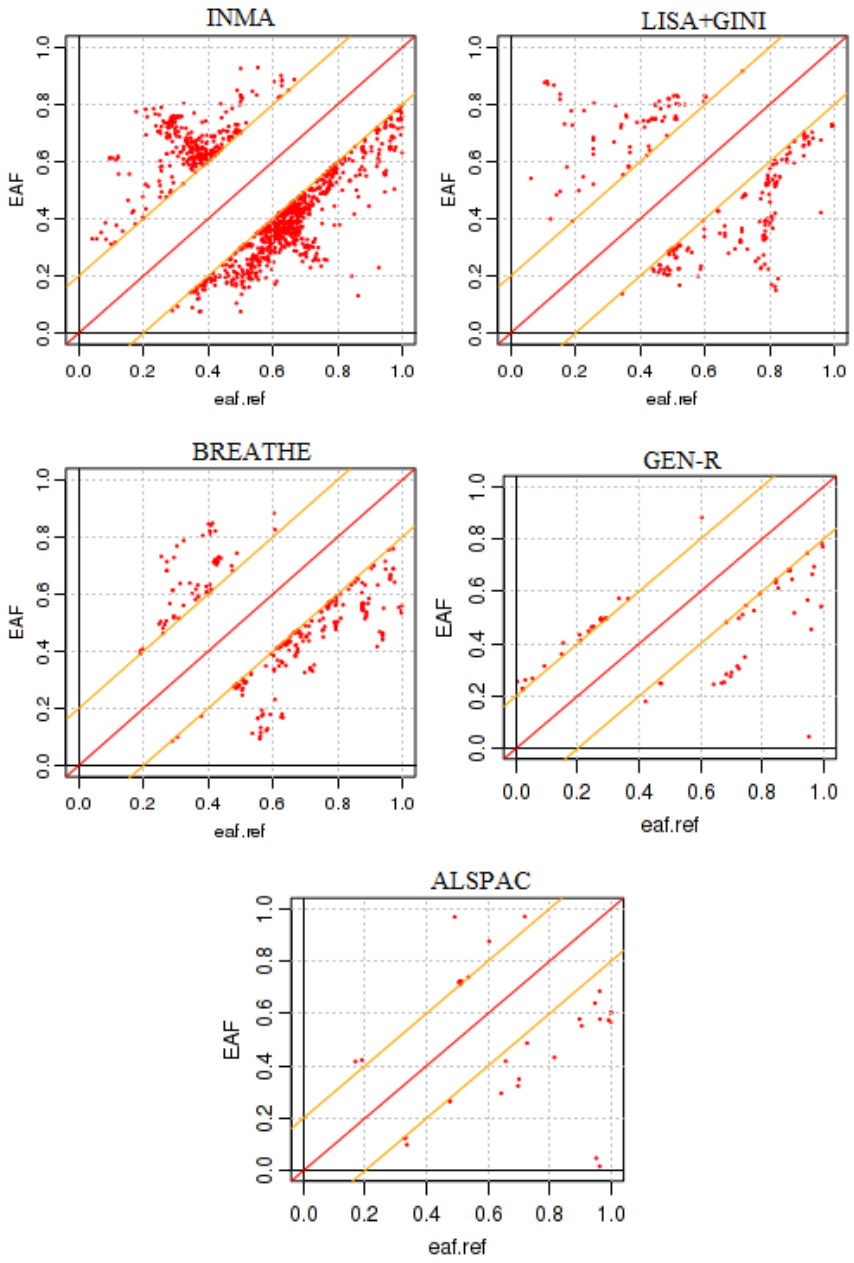

Table S2. Results of all suggestive hits (p< 1.00e-05) from GWAS meta-analysis on sleep duration in the discovery phase, BMI adjusted model (N =10,502)

SNP	Chr	Position	Allele 1/2	Frequency 1	Effect (*SE*)	Direction[a]	# hits	*meta p*	heterogeneity *p* [b]	Nearest gene
rs7121351	**11**	**72698114**	**A/G**	**0.89**	**-0.08 (0.01)**	**-----**	**9**	**2.29e-08**	**.24**	***ARAP1***
rs35630915	1	23180489	A/G	0.19	0.07 (0.01)	-----	74	3.08e-07	.50	*LUZP1*
rs157274	3	137813539	T/C	0.49	-0.04 (0.01)	-----	1	1.16e-06	.20	*SOX14*
rs9819008	3	39581	T/C	0.86	-0.09 (0.02)	----?	2	1.18e-06	.21	*LOC642891*
chr12:73456456:I	12	73456456	D/I	0.72	-0.10 (0.02)	?-?--	1	1.54e-06	.46	NA
chr6:23513559:D	6	23513559	D/I	0.21	-0.11 (0.02)	?-?--	3	1.62e-06	.58	NA
rs1230545	7	52725576	A/C	0.20	0.05 (0.01)	+++?+	2	1.81e-06	.86	*LOC100131871*
rs77543094	19	17644050	A/T	0.91	0.09 (0.02)	+++-?	3	1.86e-06	.13	*FAM129C*
rs60198202	9	28374228	A/G	0.51	-0.04 (0.01)	---+-	19	1.98e-06	.15	*LINGO2*
chr2:226028285:D	2	226028285	D/I	0.56	0.09 (0.02)	?+?++	3	3.52e-06	.42	*NYAP2*
rs143415644	12	104391449	T/C	0.05	0.09 (0.02)	+++??	2	3.60e-06	.53	*GLT8D2*
rs12539717	7	47322289	T/C	0.70	-0.05 (0.01)	-----	12	3.77e-06	.78	*TNS3*
rs190524676	15	75716731	T/G	0.90	0.10 (0.02)	++++?	1	4.25e-06	.67	*SIN3A*
rs272021	2	115886612	A/G	0.27	0.06 (0.01)	+++?+	1	4.73e-06	.18	*DPP10*
rs4509077	5	133888303	A/C	0.34	-0.04 (0.01)	-----	1	5.68e-06	.92	*FSTL4*
rs4791184	17	67741686	T/C	0.22	-0.07 (0.02)	-----	2	7.47e-06	.17	*NOL11*
rs7824578	8	8879193	A/T	0.10	-0.09 (0.02)	----?	1	7.54e-06	.98	*MFHAS1*
rs72788412	16	48650645	C/G	0.13	-0.06 (0.01)	-----	1	9.18e-06	.51	*LOC105371240*

Note: Chr= chromosome, NA, ?=not available

[a]order of participating cohorts: ALSPAC, GEN-R, LISA+GINI, INMA, BREATHE

[b]*p* value showing heterogeneity between the cohorts

Table S3a. Results of the replication analysis of the top SNP (rs74506765, chromosome 11q13.4) derived from the GWAS meta-analysis on sleep duration in children (discovery phase)

Cohort	**Allele 1/2**	**Frequency 1**	**Effect**	***SE***	***p-value***	***N***
ABCD	C/G	0.08	0.01	0.08	0.95	929
GLAKU	C/G	0.04	-0.27	0.11	0.015	321

Table S3b. Results of the replication analysis of proxies to the top SNP (rs74506765, chromosome 11q13.4) derived from the GWAS meta-analysis on sleep duration in adults (summary statistics available by Gottlieb et al, 2014[19])

SNP	**Chr**	**Position**	**Allele1/2**	**Frequency 1**	**RSquared***	***Effect***	***SE***	***p-value***	***N***
rs7121351	11	72698114	A/G	0.84	0.93	0.02	0.01	0.07	38,398
rs10898869	11	72720908	T/C	0.08	0.85	0.07	0.06	0.25	3,574
rs10751211	11	72694178	T/C	0.23	0.53	-0.02	0.01	0.14	38,394
rs1157343	11	72718096	A/G	0.35	0.21	-0.01	0.01	0.47	38,417

*it refers to the LD threshold with the top SNP (rs74506765)

Table S4. Enriched tissues/cell types identified with DEPICT associated with sleep duration in children (only nominally associated shown)

MeSH term	Name	MeSH first level term	MeSH second level term	*p*	FDR
A10.165.450	Granulation Tissue	Tissues	Connective Tissue	0.05	> 0.20
A10.165.450.300	Cicatrix	Tissues	ConnectiveTissue	0.05	> 0.20
A05.360.319.114.630.535	Ovarian Follicle	Urogenital System	Genitalia	0.05	> 0.20
A11.436.329	Granulosa Cells	Cells	Epithelial Cells	0.05	> 0.20
A06.407.312.497.535.300.500	Cumulus Cells (ovarian)	Endocrine System	Endocrine Glands	0.05	> 0.20

Note: MeSH term= Medical Subject Headings term, FDR= False Discovery Rate

Table S5. Top 10 enriched gene-sets identified with DEPICT

Original gene set ID	Original gene set description	*p*	FDR
MP:0004984	increasedosteoclastcellnumber	6.60E-06	> 0.20
MP:0008088	abnormal T-helper 1 cell differentiation	7.52E-06	> 0.20
ENSG00000160007	ARHGAP35 PPI subnetwork	7.44E-05	> 0.20
ENSG00000162407	PPAP2B PPI subnetwork	7.55E-05	> 0.20
ENSG00000162909	CAPN2 PPI subnetwork	8.70E-05	> 0.20
ENSG00000100811	YY1 PPI subnetwork	1.39E-04	> 0.20
ENSG00000106123	EPHB6 PPI subnetwork	1.50E-04	> 0.20
GO:0030888	regulation of B cell proliferation	2.49E-04	> 0.20
ENSG00000115392	FANCL PPI subnetwork	3.25E-04	> 0.20
REACTOME_SIGNAL_ATTENUATION	Attenuation of insulin receptor signalling	3.71E-04	> 0.20

Note: FDR= False Discovery Rate

Figure S3. Manhattan plot of the GWAS meta-analysis of sleep duration in children for the BMI adjusted model (*N*=10,502). The x-axis represents the autosomal chromosomes and the y-axis represents the $-\log_{10}(p)$. The red line indicates genome-wide significance (p=5.00e-08) and the blue line indicates suggestive genome-wide significance (p=1.00e-05)

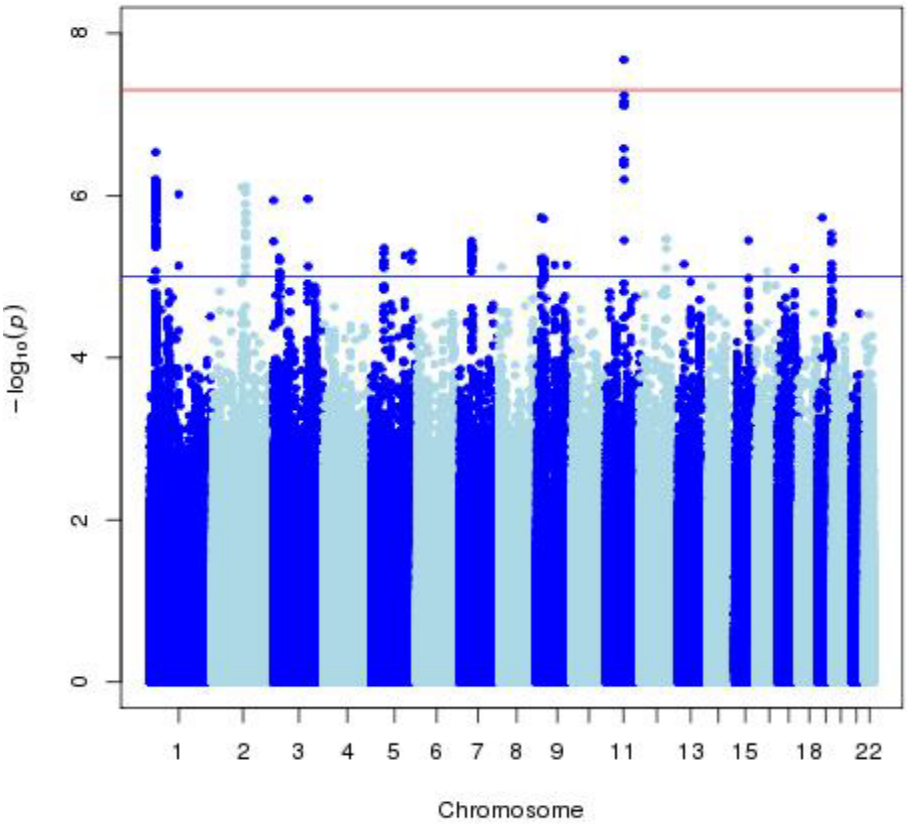

Figure S4. Quantile-quantile (QQ) plot showing the probability values from GWAS meta-analysis of sleep duration for the BMI adjusted model (*N*=10,502). The red line indicates the distribution under the null hypothesis and the shaded area indicates the 95% confidence band

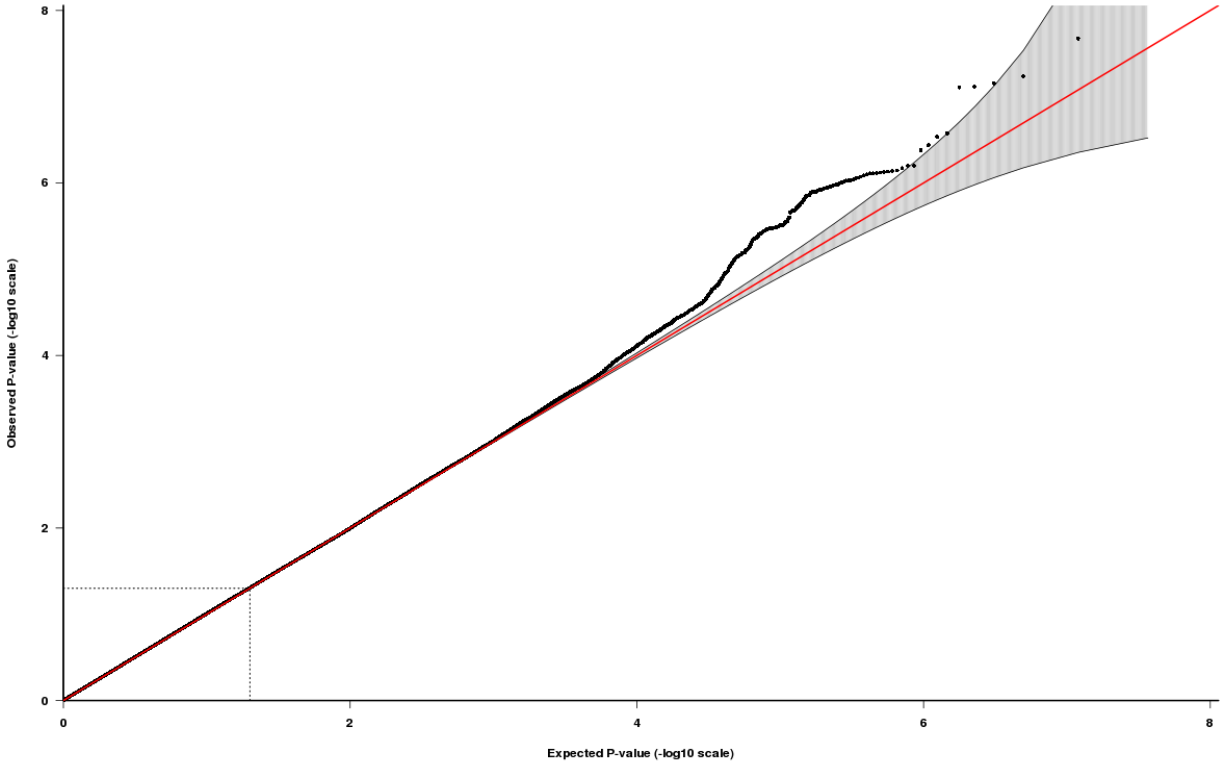

Table S6. Genetic correlations between sleep duration in children (derived from the GWAS summary statistics of the current study, under the BMI adjusted model) and common metabolic and psychiatric traits, using LD score regression and GWAS summary statistics data available in the literature

		Sleep duration in children	
Traits	***N***	r_G **(*se*)**	***p***
Sleep duration (adults)[19]	47,180	.15 (0.17)	0.37
Metabolic			
Obesity (children)[20]	13,848	.06 (0.11)	0.60
Type 2 diabetes (adults)[21]	**69,033**	**.23 (0.11)**	**0.04**
2hrs glucose (adults)[22]	46,186	.38 (0.22)	0.09
Psychiatric			
bipolar disorder (adults)[23]	16,731	.05 (0.14)	0.74
major depression (adults)[24]	18,759	.05 (0.17)	0.79
schizophrenia (adults)[25]	70,100	-.05 (0.11)	0.63
ADHD (children/family trios)[26]	3,351	.42 (0.26)	0.12

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*Amsterdam Born Children and their Development (**ABCD**)*

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*Avon Longitudinal Study of Parents and Children (**ALSPAC**)*

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*Brain development and Air pollution ultrafine particles in school children (**BREATHE**)*

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*Generation R Study (**GEN-R**)*

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Glycyrrhizin in Licorice (GLAKU)

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*Lifestyle-Immune System- Allergy Study and German Infant Study on the Influence of Nutrition Intervention (**LISA+GINI**)*

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*Infancia y media ambiente project (**INMA**)*

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