Supplemental material

Examining the contribution of birth weight to mental health, cognitive, and socioeconomic outcomes: A two sample Mendelian randomization

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eIntroduction

Evidence before this study: additional detailed information from a systematic search

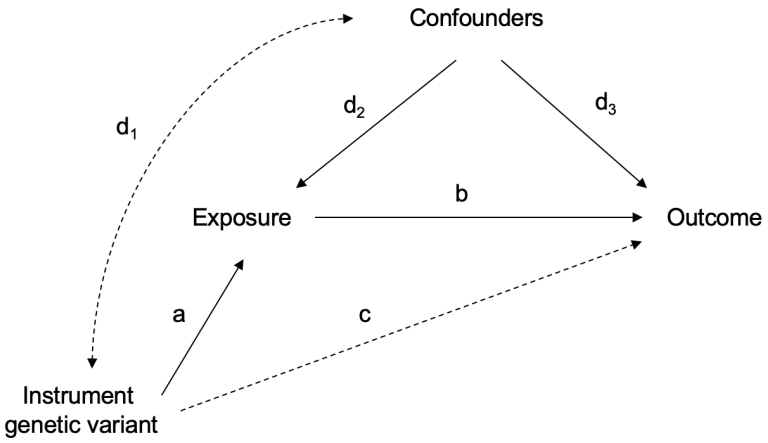
We systematically searched Medline without date limitations up to April 30, 2019 (updated on July 16, 2019), using the following keywords: ("Mental Health"[Mesh] OR "Substance-Related Disorders"[Mesh] OR "Smoking"[Mesh] OR suicid* OR "suicide attempt" OR "social class"[Mesh] OR "Social Welfare"[Mesh] OR Education[Mesh] OR "Cognitive Dysfunction"[Mesh] OR "Intelligence"[Mesh]) AND ("birth weight" OR "birthweight" OR "fetal growth" OR "low birth weight" OR "low birthweight"). One researcher searched among the 7635 retrieved articles (filters were: English, Humans, Journal article) for pertinent articles reporting on the association between birth weight and later mental health, cognitive, and socioeconomic outcomes. Additionally, manual search on key journals was performed. Most of the available evidence came from studies using classic epidemiological designs (eg, cohort study, registers), including meta-analysis of observational studies. Overall, studies suggested associations of low birth weight with higher risk of psychiatric disorders such as depression, schizophrenia, suicidal behavior, ADHD, intelligence, socioeconomic status (eg, (1–11)). However, a number of studies failed to find associations, and the overall evidence resulted contradictory. For example, of two meta-analyses on the association between birth weight and depression, only one found evidence of increased risk of adult depression for low birth weight children (6, 12). Only few studies (mainly from northern European countries and the United Kingdom) relied on quasi-experimental designs to investigate the association between birth weight and various mental health problems (eg, (4, 13, 14)). These studies found that most of these associations were no longer significant using robust designs such as twin or sibling comparison. For example, a Swedish study found that while nine outcomes were significantly associated with birth weight in the population at large, only three (depression, ADHD and autism spectrum disorders) remained associated when a within-sibling design was used (4). The association between birth weight and ADHD was the most consistently reported across studies using classic observational (15, 16), sibling (4), and twin designs (13). Only one previous study used a Mendelian randomization design (17). This study investigated the association of birth weight with ADHD, major depressive disorder, and schizophrenia, reporting no evidence for a contribution of birth weight to these outcomes. However, this study did not take into account the confounding effect of maternal genotype when used individual's SNPs as instruments for birth weight. We found no study using Mendelian randomization to investigate the association between birth weight and cognitive or socioeconomic outcomes.

eMethods

Mendelian randomization: method and assumptions

A schematic representation of the Mendelian randomization (MR) model is presented in **eFigure 1**. In two-sample MR, association between the instrument genetic variant(s) and the exposure comes from a GWAS, and the association between these same genetic variant(s) and the Outcome come from a different GWAS. The unconfounded association of the Exposure with the Outcome (*b* in the figure) is estimated as c/a.

eFigure 1. Mendelian randomization model



The same assumption as other instrumental variable approaches held for Mendelian randomization analyses. These are the following:

Relevance. The instrument used must be robustly associated with the exposure. In our study, we selected 48 SNPs as instruments of birth weight. These were selected from an initial pool of 209 SNPs showing genome wide statistical significance ($P < 6.6\times10^{-9}$) in the birth weight GWAS, and still maintained statistical significance ($P < 1\times10^{-6}$) once adjusted for the correlated maternal effect. The validity of the instrument can be quantified using the *F* statistic, with $F > 10$ indicating strong instruments. The *F* statistics for our instrument ranged from 19 to 182 (median, 28; mean, 36), suggesting that all SNPs were strong instruments.

Exchangeability. Instruments must be independent from confounding of the exposure-outcome association (d_1 non-significant). This assumption is not empirically testable in two-sample MR. However, we conducted a search in the phenoScanner database to verify whether, in the literature, the SNPs instruments have been associated with traits likely to be considered confounders of the exposure-outcome association.

Exclusion restriction criterion. There is no association between the instrument and the outcome conditional on the exposure. Differently said, the only pathway of association of the instrument to the outcome must be the trough the

exposure. This assumption may be violated by the pleiotropic effects of the SNPs used as instruments (or those in linkage disequilibrium with them). Pleiotropy refers to the effect of a SNP on multiple traits/genes, and can be distinguished in horizontal and vertical pleiotropy. Horizontal pleiotropy refers to the association of the instrument SNPs with traits/genes that can potentially open alternative pathways through which the instruments may be associated with the outcome, and that are not in the causal pathway between the instruments and the outcome. Horizontal pleiotropy, if unbalanced, violates the exclusion restriction criterion. Vertical pleiotropy refers to the association of the instrument SNPs with traits/genes that can are in the causal pathway between the instruments and the outcome. For example, when studying the association between birth weight and ADHD, vertical pleiotropy would be represented by the association between the instruments SNPs and intelligence, which in turn is associated with ADHD. Vertical pleiotropy does not violate the exclusion restriction criterion. To evaluate the possible violation of this assumption, we used 3 strategies. First, we evaluate the presence of unbalanced horizontal pleiotropy by testing the significance of the intercept of the MR-Egger regression, and evaluating the presence of heterogeneity using the *Q* statistic. Second, we used a range of sensitivity analyses in addition to our primary MR analyses; all these methods differ in the assumptions regarding horizontal pleiotropy. Third, we conducted a search in the PhenoScanner database to find the traits that have been associated with each SNP instrument (and the SNPs in linkage disequilibrium, $r^2 \geq .80$) in the literature.

F statistic

The r^2 and F statistic for each SNP are reported in the table below:

eTable 1. F statistic and r^2 for each SNP

SNP	r2	F
rs1012167	0.00058	36.00
rs10181515	0.00130	26.45
rs10265057	0.00078	31.36
rs10935733	0.00044	27.56
rs11042596	0.00073	45.56
rs11055030	0.00048	19.36
rs11096402	0.00048	30.25
rs112139215	0.00314	49.00
rs1129156	0.00048	19.36
rs116807401	0.00774	30.25
rs11698914	0.00084	33.64
rs11711420	0.00048	19.36
rs12401656	0.00084	23.36
rs13266210	0.00090	36.00
rs134594	0.00048	30.25
rs138715366	0.05523	114.10
rs1480470	0.00078	49.00
rs1482852	0.00292	182.25
rs1547669	0.00032	20.25
rs222857	0.00068	42.25
rs2282978	0.00044	27.56
rs2551347	0.00084	33.64
rs28457693	0.00160	32.65
rs28505901	0.00058	23.04
rs3933326	0.00053	33.06
rs41311445	0.00116	23.59
rs41355649	0.00176	27.56
rs4144829	0.00102	40.96
rs4444073	0.00053	33.06
rs4511593	0.00036	22.56
rs4953353	0.00036	22.56
rs56188432	0.06250	26.03
rs6575803	0.00116	23.59
rs6930558	0.00048	19.36
rs7076938	0.00084	33.64
rs72681869	0.01166	26.45
rs73143584	0.00096	19.61
rs732563	0.00036	22.56
rs7402983	0.00073	45.56
rs753381	0.00032	20.25
rs754868	0.00036	22.56
rs7772579	0.00073	29.16
rs7819593	0.00053	21.16
rs7968682	0.00137	85.56
rs80278614	0.00270	33.38
rs8106042	0.00053	21.16
rs8756	0.00137	85.56
rs9909342	0.00036	22.56
Sum	0.17579	1744.05

Fetal and maternal effects on birth weight

Associations between individual's genetic variants and birth weight may result from (i) the direct effect of the individual's own genotype on their birth weight, (ii) the effect of the maternal genotype on the individual's birth weight, i.e. the maternal genotype (or behavior depending on maternal genotype) influencing the intrauterine environment, in turn influencing birth weight, (iii) the combination of both (same gene having both fetal and maternal effect, either in the same direction or in opposite directions). Such multiple sources of variation in birth weight must be taken into account to study the genetic association between birth weight and later outcomes. Indeed, the correlation (r~0.5) between an individual's genotype and his/her mother's genotype may introduce confounding effects due to the indirect effect of maternal genotype on the intrauterine environment. To estimate the unbiased effect of the individual's genotype on his/her own birth weight, a structural equation model has been proposed and implemented in a large GWAS. This model allows one to statistically adjust the influence of genetic variants on the individual genotype for the maternal effect on birth weight taking into account the correlation between the 2 genotypes. Details on the model can be found elsewhere (18, 19). In this study, we selected as instruments the SNPs having a fetal effect only, and the beta value for the association was adjusted for the correlated maternal effect.

Power analysis

Formulas are available to estimate the power of one-sample Mendelian randomization analysis. However, to our knowledge, there is no formula allowing one to estimate the power in a two-sample Mendelian randomization analysis. We therefore estimated our statistical power considering the sample size of the SNP-outcome GWAS, because the hypothesis testing refers to a difference in the outcome according to the level of the exposure (birth weight). The results of the power calculation are presented in **eTable 2**. For categorical outcomes, we reported the power given by our sample size to detect 20%, 30%, and 40% difference (ie, OR 1.20/0.80, 1.30/0.70, and 1.40/0.60, respectively) in the risk of the outcome per 1 SD-unit increase in the exposure. For continuous outcomes, we reported the power given by our sample size to detect 20%, 30%, and 40% of a SD in the outcome per 1 SD-unit increase in the exposure. Analyses were performed using the web application: https://sb452.shinyapps.io/power/.

These analyses suggested for all outcomes adequate power (ie, ≥ 90%) to detect associations as small as 20% change in the outcome for 1-SD unit change in the birth weight.

eTable 2. Power analysis

Trait	N	Cases/controls ratio	Power (%) to detect the following OR		
			1.2	1.3	1.4
ADHD	53293	0.56	100	100	100
Autism Spectrum Disorder	46350	0.66	100	100	100
Bipolar Disorder	46582	0.65	99.9	100	100
Major Depression Disorder	173005	0.53	100	100	100
Obsessive-Compulsive Disorder	9725	0.38	92.6	99.8	100
Post-Traumatic Stress Disorder	9537	0.34	90.8	99.7	95.7
Schizophrenia	105318	0.63	100	100	100
Suicide attempt	50264	0.14	100	100	100
Intelligence	264498	-	100	100	100
Educational attainment	264498	-	100	100	100
Income	96900	-	100	100	100
Social deprivation	112005	-	100	100	100

ADHD, Attention-Deficit/Hyperactivity Disorder

Details on samples overlap

In two-sample Mendelian randomization, bias may emerge from the overlap between the instrument-exposure and instrument-outcome datasets. Overlap for outcomes such as ADHD, Educational attainment, Intelligence, Income, and Social deprivation is present. The bias on the MR estimate due to the overlap has been quantified as explained by Burgess, Davies, and Thompson (20) and using the web application: https://sb452.shinyapps.io/overlap/. We estimated the bias under 2 hypothetical situations (i) with a bias of the observational estimate of 0.4 per standard deviation change in the risk factor, and (ii) with a bias of the observational estimate of 0.8 per standard deviation change in the risk factor. Additionally, as precisely calculating the proportion of overlap is not possible with summary statistics, we calculate the bias for all ranges of overlap up until complete (100%) overlap. We calculate the bias for the smallest sample among our outcomes. The analyses suggest virtually no bias, with no inflation of type I error, even in the case of total overlap between samples (**eTable 3**).

eTable 3. Potential bias due to samples overlap

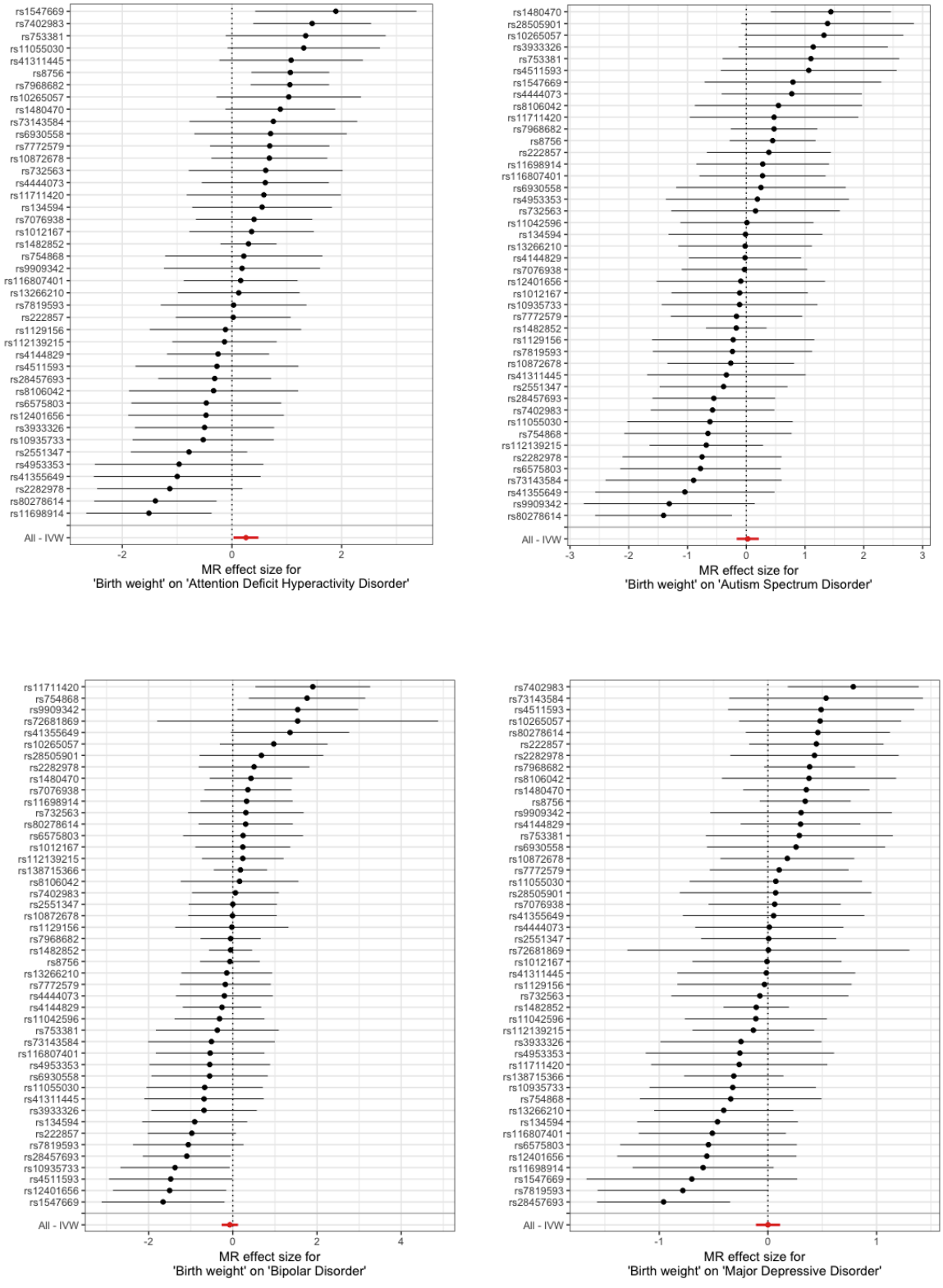
Smallest N among the analyzed outcome	Overlap proportion	Bias of the observational estimate, 0.4		Bias of the observational estimate, 0.8	
		Bias MR estimate	Type I Error	Bias MR estimate	Type I Error
Binary outcome, N=9537	0	0.000	0.05	0.000	0.05
	0.1	0.000	0.05	0.000	0.05
	0.2	0.000	0.05	0.000	0.05
	0.3	0.000	0.05	0.000	0.05
	0.4	0.000	0.05	0.000	0.05
	0.5	0.000	0.05	0.000	0.05
	0.6	0.000	0.05	0.000	0.05
	0.7	0.000	0.05	0.000	0.05
	0.8	0.000	0.05	0.000	0.05
	0.9	0.000	0.05	0.000	0.05
	1	0.000	0.05	0.000	0.05
Continuous outcome, N=96900	0	0.000	0.05	0.000	0.05
	0.1	0.000	0.05	0.000	0.05
	0.2	0.000	0.05	0.000	0.05
	0.3	0.000	0.05	0.000	0.05
	0.4	0.000	0.05	0.000	0.05
	0.5	0.000	0.05	0.000	0.05
	0.6	0.000	0.05	0.000	0.05
	0.7	0.000	0.05	0.000	0.05
	0.8	0.000	0.05	0.000	0.05
	0.9	0.000	0.05	0.000	0.05
	1	0.000	0.05	0.000	0.05

eResults

Single SNP effects

The forest plots in the figure show, for each outcome, the Wald estimate for each single SNPs, as well as the pooled Inverse-Variance Weighted (IVW) effect (in red).

eFigure 2. Forest plot reporting Single SNP effects



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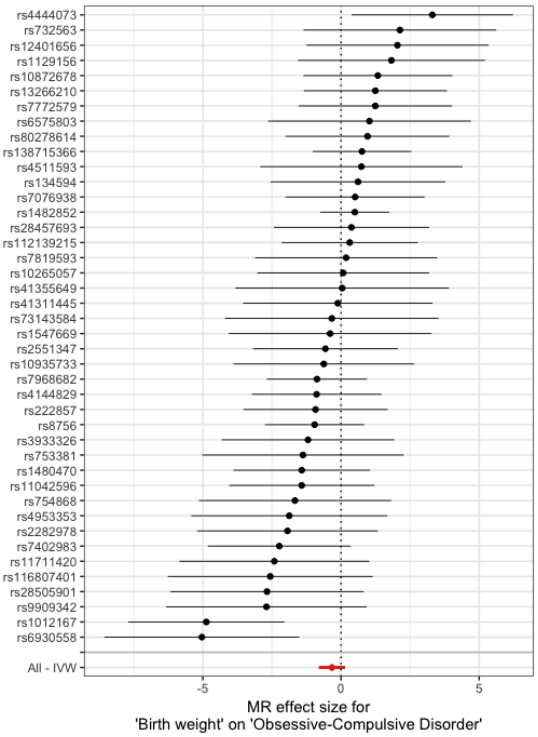

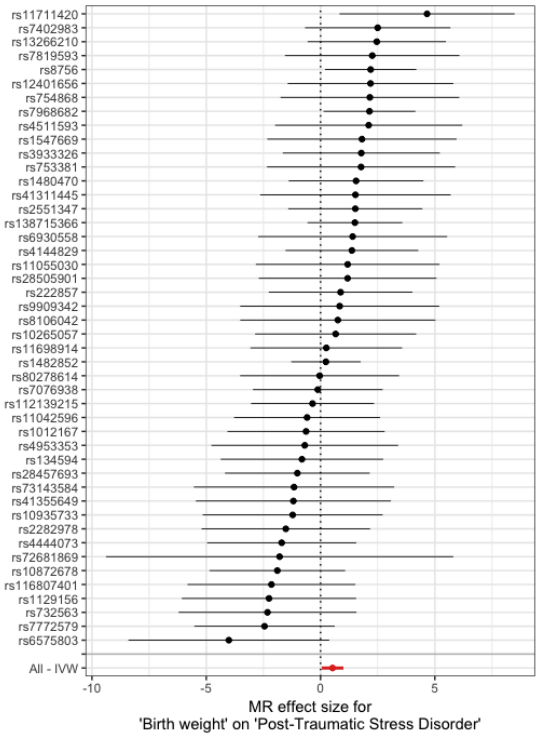

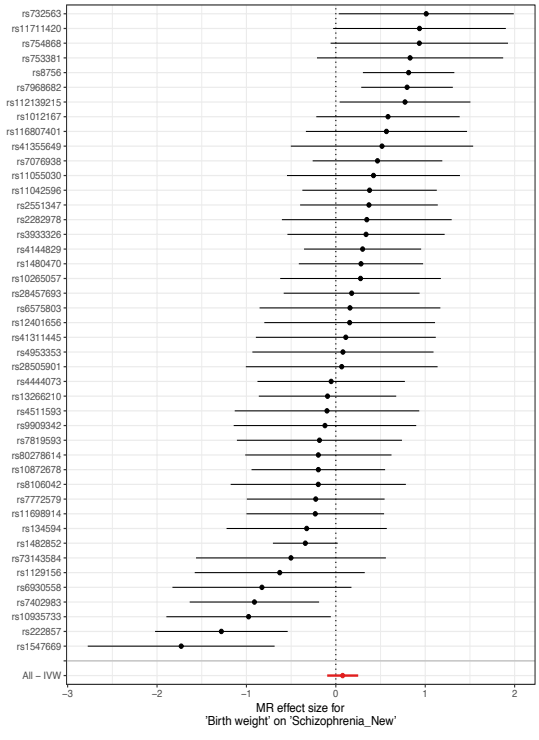

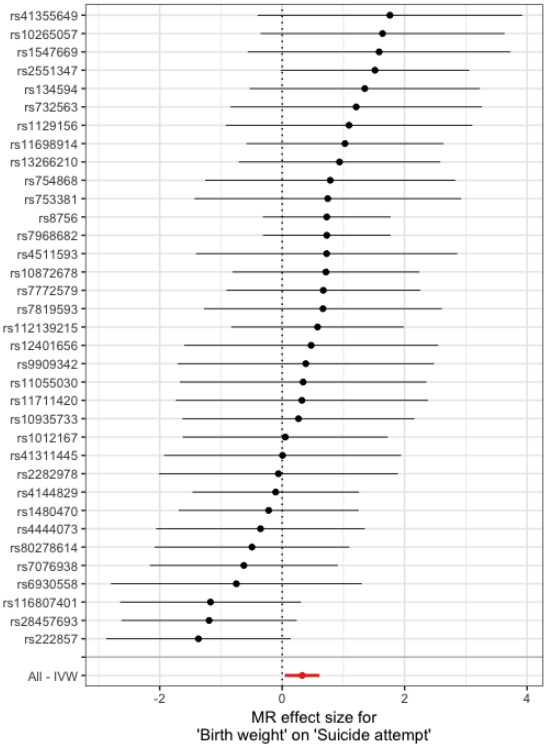

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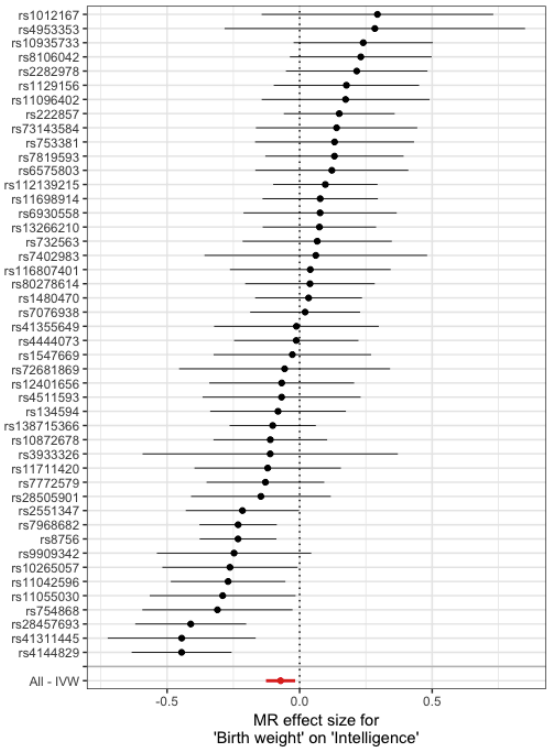
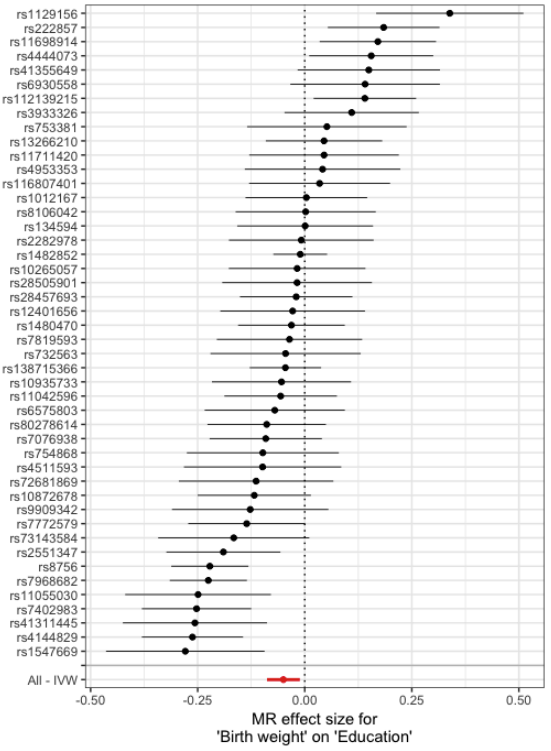
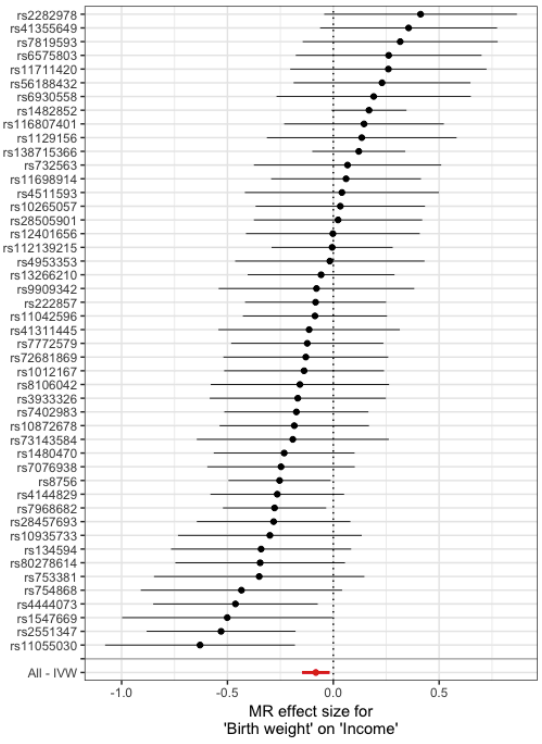
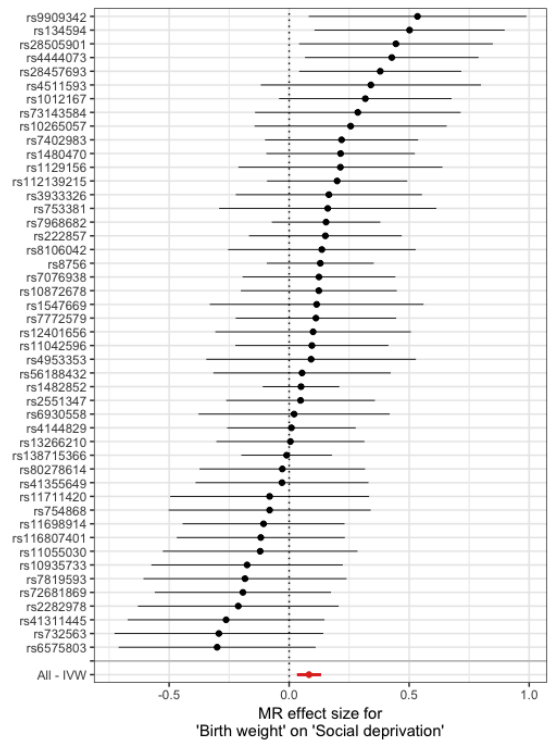








Results of the tests for pleiotropy

The table reports the results for the heterogeneity test (Q statistics) and the test of the MR-Egger intercept (unbalanced horizontal pleiotropy test).

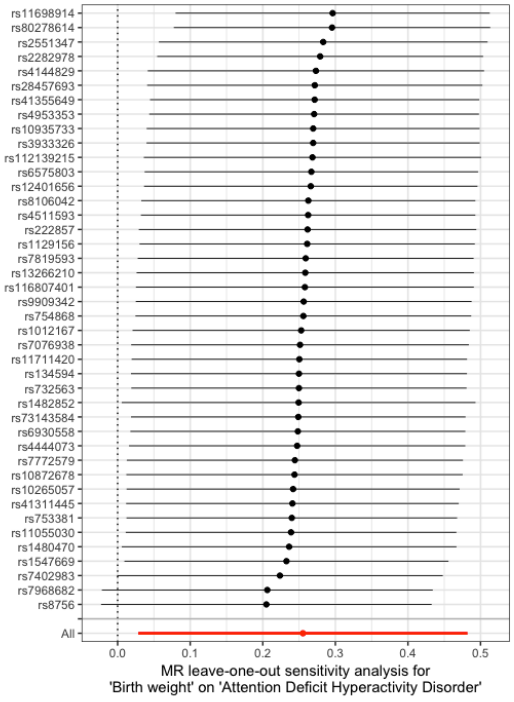
eTable 4. Results of the tests for pleiotropy

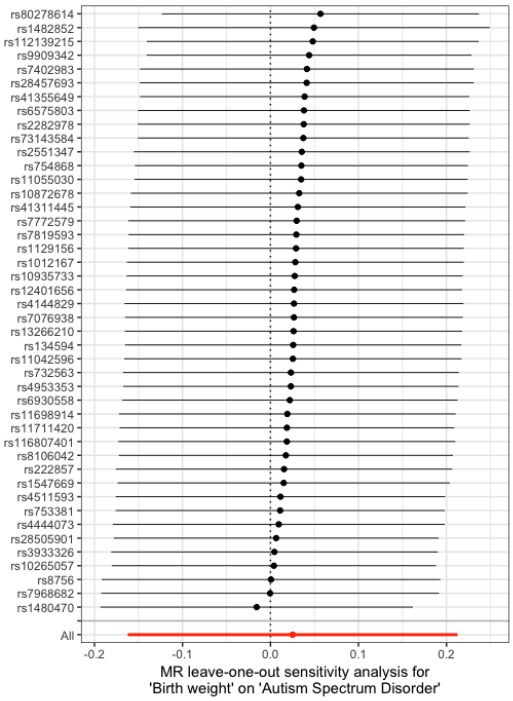
	Q statistic		MR-Egger intercept		
Outcome	***Q* value (DF)**	***P***	**MR-Egger intercept**	**SE**	***P***
Attention-Deficit/Hyperactivity Disorder	71.49 (41)	0.002	0.00	0.01	0.653
Autism Spectrum Disorder	51.42 (43)	0.177	-0.01	0.01	0.157
Bipolar Disorder	64.77 (45)	0.028	0.01	0.01	0.404
Major Depressive Disorder	59.36 (45)	0.074	0.00	0.00	0.433
Obsessive-Compulsive Disorder	52.25 (41)	0.112	0.03	0.02	0.078
Post-Traumatic Stress Disorder	44.78 (45)	0.481	0.00	0.02	0.957
Schizophrenia	90.42 (43)	<0.001	0.00	0.01	0.373
Suicide attempt	31.51 (34)	0.590	-0.02	0.01	0.172
Intelligence	104.79 (45)	<0.001	0.00	0.00	0.123
Educational attainment	161.93 (45)	<0.001	0.00	0.00	0.741
Income	70.75 (46)	0.011	0.01	0.00	0.024
Social deprivation	49.09 (46)	0.350	0.00	0.00	0.148

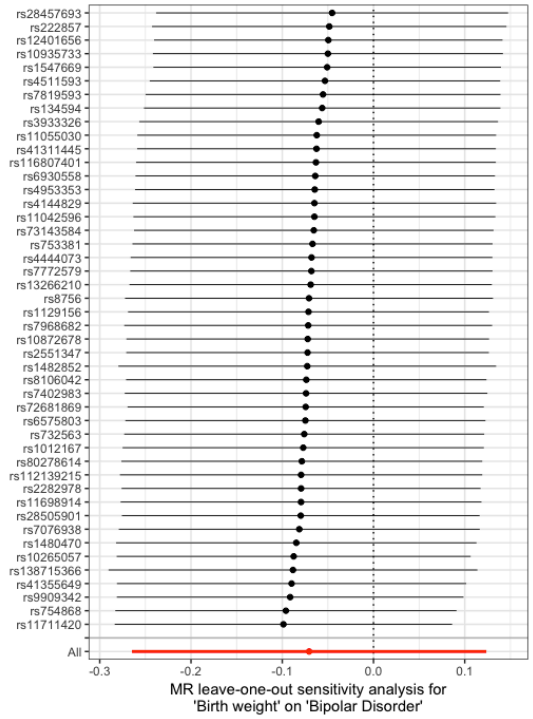
Leave-one-out analysis

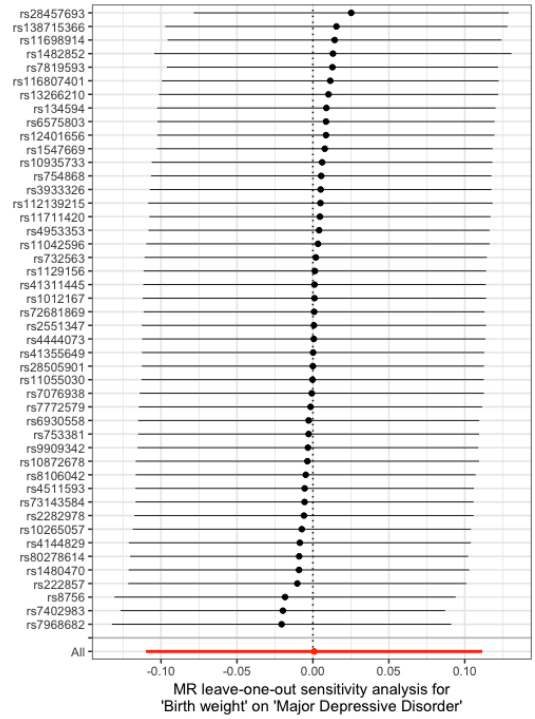
The forest plots in **eFigure 3** show, for each outcome, the Inverse-Variance Weighted (IVW) estimate calculated excluding one SNP instrument at the time, as well as the IVW instrument obtained considering all available SNP instruments (in red).

eFigure 3. Forest plots for the leave-one-out analysis









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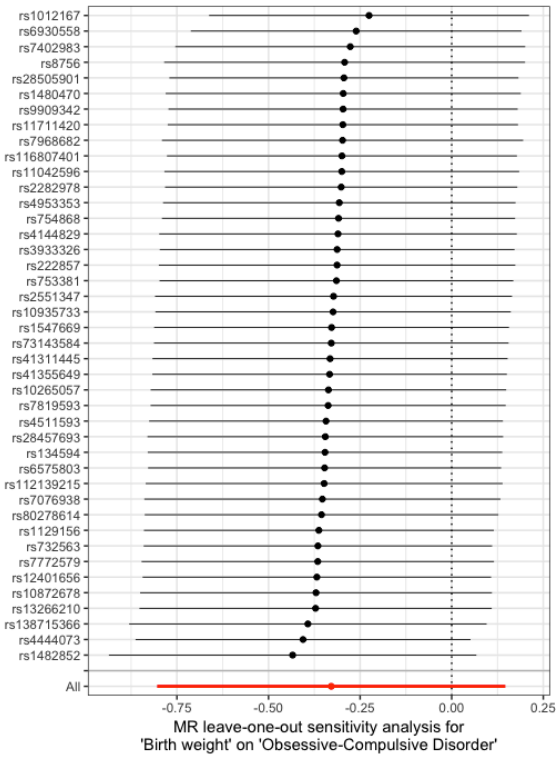

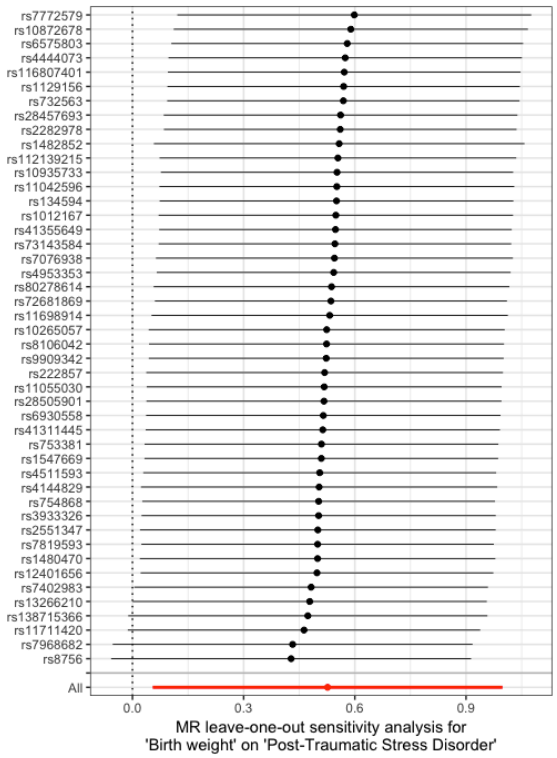

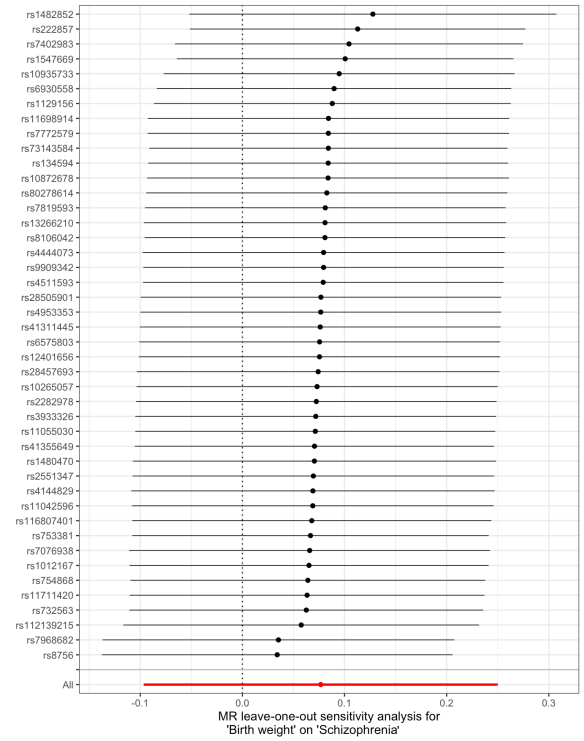

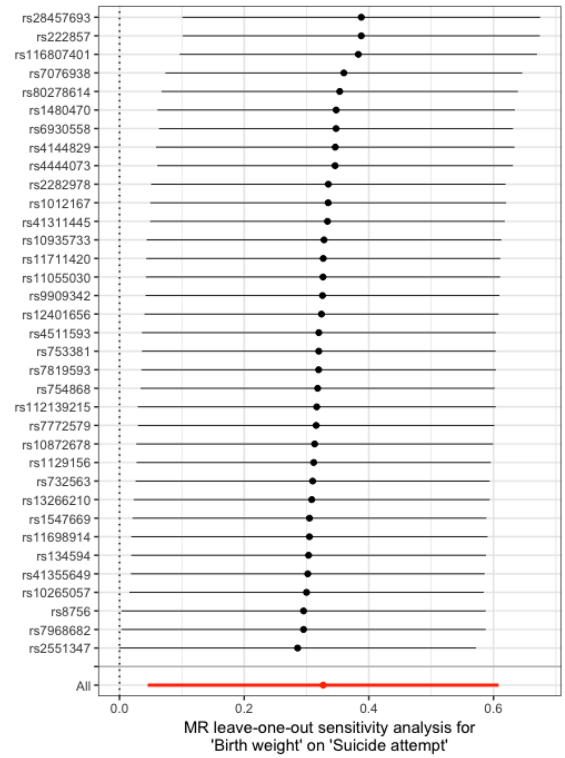

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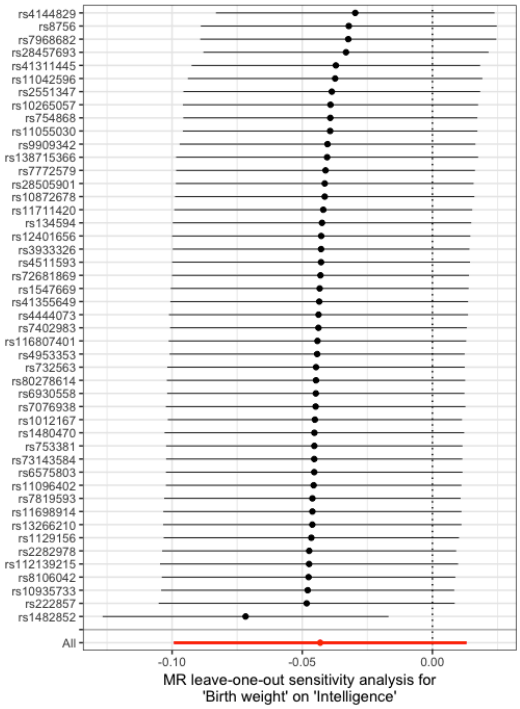
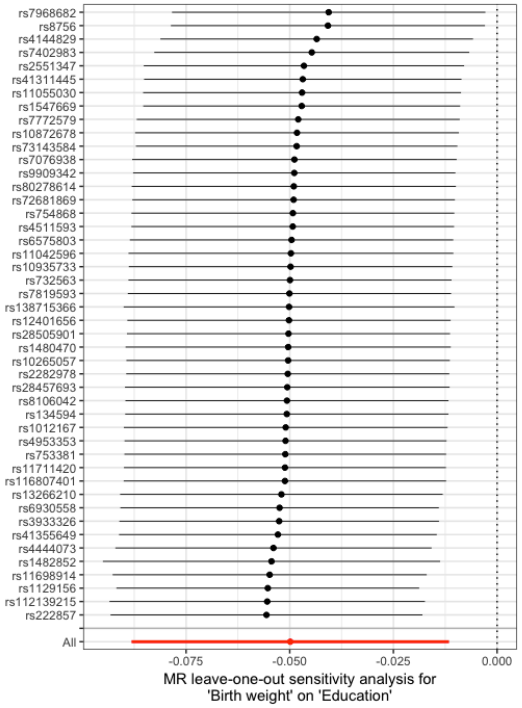
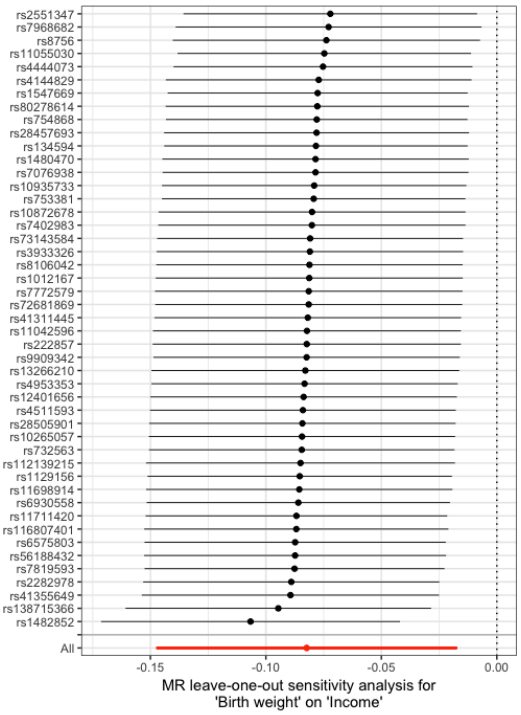
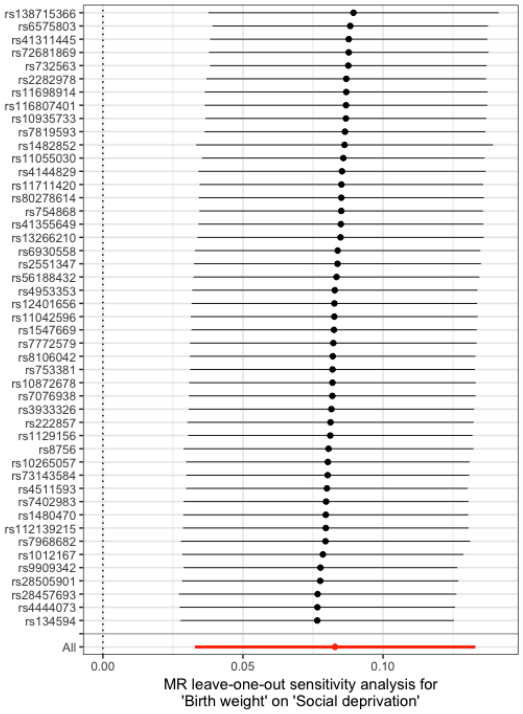








PhenoScanner Search

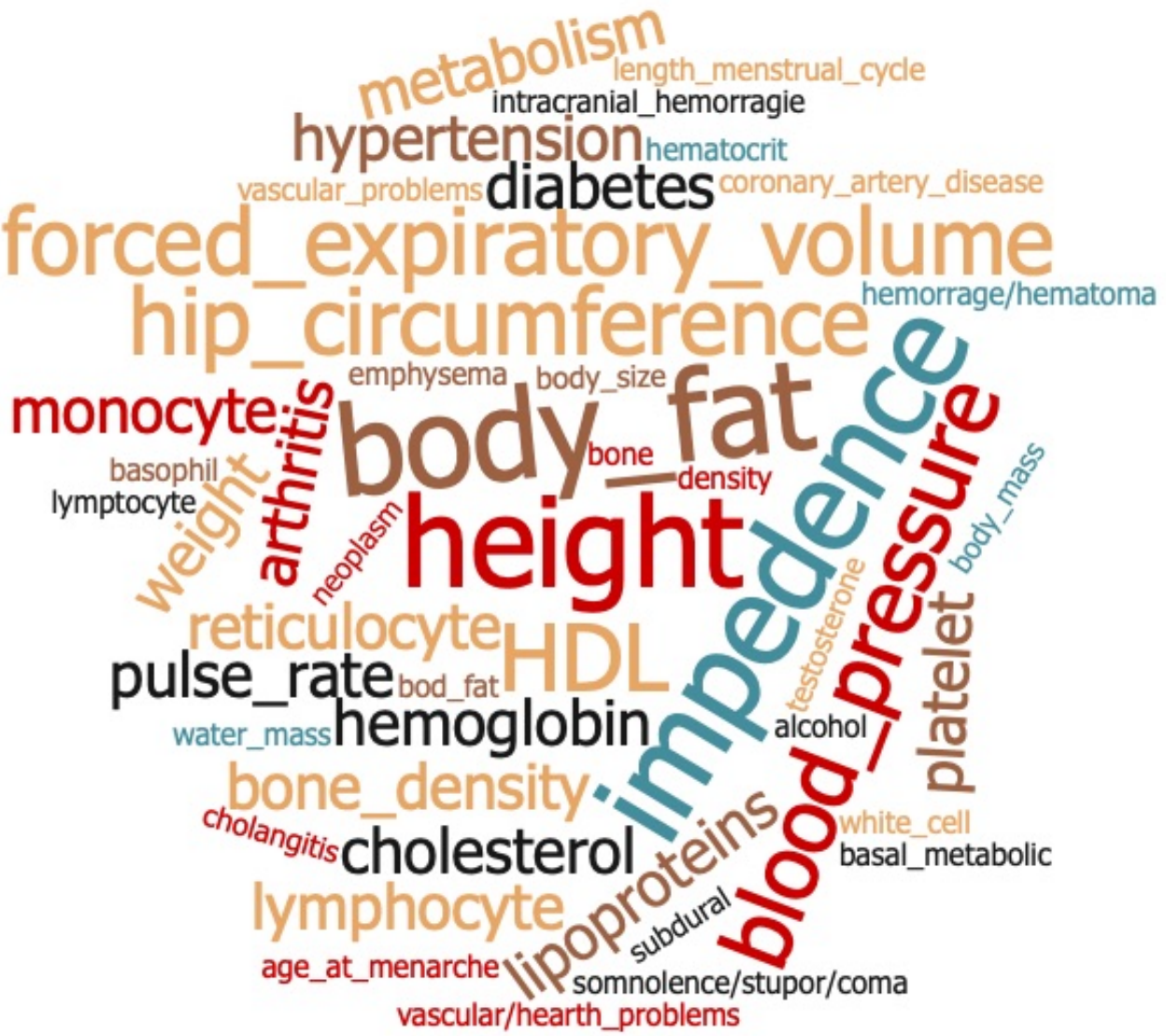
The PhenoScanner database was searched to identify the known association between the SNP instruments (and those in linkage disequilibrium with $r^2 \geq 0.80$) and traits explored in the literature. The aim was to identify potential source of horizontal pleiotropy or potential associations with traits that can confound the exposure-outcome association. Findings (ie, the traits associated with the SNPs of interest according to the phenoScanner search) are visualized in **eFigure 4** using a word cloud in which the dimension of each word (ie, trait) is proportional to the number of SNPs associated with that trait.

eTable 4. Results of the PhenoScanner Seach

SNP	CHR	Function	Gene	Associated traits
rs1012167	20	intergenic	LINC01728	Cholesterol, lipoproteins, body fat
rs10181515	2	intergenic	NEU2	Impedance, body fat
rs10265057	7	intergenic	TNS3	
rs10935733	3	intron	RP11-680B3.2	
rs11042596	11	intergenic	IGF2	Height, length menstrual cycle
rs11055030	12	upstream	APOLD1	Height, lymphocyte count, metabolism, body fat, hypertension
rs11096402	X	intron	PLAC1	
rs112139215	7	intron	MLXIPL	
rs1129156	19	synonym	MAP3K10	pulse rate
rs116807401	4	missense	PABPC4L	Height, body mass
rs11698914	20	intron	COMMD7	Height, monocyte count, basophil count
rs11711420	3	upstream	KLHL24	Weight, body fat
rs12401656	1	upstream	RNU6-880P	
rs13266210	8	int	ANK	Diabetes, Reticulocyte
rs134594	22	upstream	KREMEN1	Bone density, Reticulocyte, arm impedance
rs138715366	7	intron	YKT6	Subdural hemorrhage/hematoma
rs1480470	12	intergenic	RP11-366L20.4	Body fat, pulse rate
rs1482852	3	upstream	LINC02029	Height, body fat, waist circumference, high-density lipoprotein, age at menarche, hemoglobin
rs1547669	6	-	-	Height, rheumatoid arthritis, Plateletcrit, platelet count, alcohol intake past 10 years
rs222857	-	-	-	
rs2282978	7	intron	CDK6	Height, body fat, monocyte count, blood pressure, bone density, rheumatoid arthritis
rs2551347	2	intron	KLHL29	Height, body fat, lymphocyte count, impedance, white cell count
rs28457693	9	intron	PTCH1	Height, body fat, impedance, forced expiratory volume
rs28505901	9	intron	GPSM1	Height, diabetes
rs3933326	9	intron	PHF19	
rs41311445	22	3_prime_UTR	SNU13	Body fat mass, height, impedance arm
rs41355649	19	downstream	CEBPA	Impedance, lymphocyte count
rs4144829	4	intron	LCORL	Body fat mass, height, basal metabolic rate, weight
rs4444073	11	downstream	ADM	Impedance, body fat, metabolism, height
rs4511593	17	intron	TNFSF12-TNFSF13	Impedance, blood pressure, body fat, testosterone
rs4953353	2	intron	EPAS1	
rs56188432	2	missense	ACVR1C	Neoplasm, emphysema, intracranial hemorrhage, body size, cholangitis, somnolence/stupor/coma
rs6575803	14	intron	MEG3	Body fat
rs6930558	6	-	-	
rs7076938	10	intergenic	ADRB1	Vascular/hearth problems, hypertension, high-density lipoprotein, height
rs72681869	14	missense	SOS2	Blood pressure, hip circumference, body fat, hemoglobin
rs73143584	20	intron	ZBTB46	Blood pressure, vascular problems, coronary artery disease
rs732563	8	upstream	CTC-756D1.1	Height, body fat, hip circumference
rs7402983	15	intron	IGF1R	Height, body fat, hip circumference, hip circumference, water mass, impedance
rs753381	20	missense	PLCG1	Cholesterol, lipoproteins, hematocrit
rs754868	2	intergenic	AC016735.1	Blood pressure
rs7772579	6	intron	ESR1	Bone density, HDL cholesterol
rs7819593	8	intron	ZFPM2	
rs7968682	12	intergenic	HMGA2	Height, body fat, forced expiratory volume, blood pressure
rs80278614	11	intergenic	TBX15	Height
rs8106042	19	intron	INSR	Height
rs8756	12	3_prime_UTR	HMGA2	Height, body fat, forced expiratory volume
rs9909342	7	intergenic	RP11-173M1.4	

SNP, Single Nucleotide Polymorphism; CHR, Chromosome

eFigure 4. Word cloud visualizing the results of the PheonoScanner search



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