Supplementary Material

Thompson, WD et al. *PLoS Medicine* (2019) Jun 18;16(6):e1002828: **Association of maternal circulating 25(OH)D and calcium with birth weight: A mendelian randomisation analysis;** https://doi.org/10.1371/journal.pmed.1002828

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S1 Text: Study Descriptions

UK Biobank

Between 2006 and 2010, patients were recruited from the NHS patient registers and contacted if they lived in close proximity to one of 22 assessment centres in England, Scotland and Wales. Detailed medical data was collected on 502,655 participants, aged between 40 and 69 at recruitment [1]. A total of 190,406 women in the UK Biobank cohort who had reported their first child's birth weight (BW) were included in the primary analyses of this paper. All participants provided written informed consent, including for their collected data to be used by international scientists. UK Biobank has approval from the North West Multi-centre Research Ethics Committee (MREC), which covers the UK. UK Biobank's research ethics committee and Human Tissue Authority research tissue bank approvals mean that researchers wishing to use the resource do not need separate ethics approval.

ALSPAC

Women expecting a live birth between the 1st of April 1991 and 31st of December 1992 whilst living in Avon, UK were invited to take part in the study. Initially 14,541 pregnancies were recruited, which resulted in 14,676 fetuses, 14,062 live births and 13,988 children alive after one year, with additional children being recruited later [2,3]. Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool [4]. Mothers provided written informed consent and

ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees.

EFSOCH

Between 2000 and 2004, pregnant women from a postcode defined region of Exeter, UK and their partners were recruited via the Exeter Maternity Unit database. A total of 1,017 families (98% white European) were recruited [5], from which a total of 993 live births were included in the primary analyses of this paper. All mothers and fathers gave informed consent and ethical approval was obtained from the local review committee.

S2 Text: Selecting of participants of White European ancestry

In UK Biobank, we defined a subset of "white European" ancestry participants so that only those of this ethnic background were included in our analyses. To do this, we generated ancestry principal components (PCs) in the 1000 genomes samples. The UKB samples were then projected into this PC space using the SNP loadings obtained from the principal components analysis using the 1000 genomes samples. The UK Biobank participants' ancestry was classified using K-means clustering centred on the 3 main 1000 genomes populations (European, African, South Asian). Those clustering with the European cluster were classified as having European ancestry. The UK Biobank participants were asked to report their ethnic background. Only those reporting as either "British", "Irish", "White" or "Any other white background" were included in the clustering analysis.

For ALSPAC, we also used PCs in the 1000 genomes sample to separate out white Europeans in the genotyped individuals (see above).

EFSOCH only included participants of white British origin (defined using PCs) for analyses[5]. Nonetheless, principal component analysis was performed to assess ancestry of the sample using flashPCA [6]. Outliers were defined as >4.56 SD from the cluster mean

(defined using 1000 Genomes European data as the reference) and excluded (n=21 individuals [0.76%])

S3 Text: Selecting participants for own birth weight analyses in UK Biobank

A total of 280,315 participants reported their own BW in kilograms at either the baseline visit or at least one of the follow-up visits. Participants reporting being part of a multiple birth were excluded from our analyses (N=10,057). For participants reporting BW at more than one visit (N=11,629), the average across the reported BWs were used, and if the largest difference between any 2 time points was >1kg, they were excluded (N=80). Data on gestational duration were not available. However, in order to exclude likely pre-term births, participants with BW values <2.5kg were excluded. We also excluded those with a BW >4.5kg as these are likely to be reporting errors or extreme outliers (total number excluded because of <2.5kg or >4.5kg BW =37,691). Participants' own BW was regressed against year of birth and assessment centre location. Residuals from that regression model were then used in all analyses with values converted to standard deviation units for analysis.

S4 Text: Measuring 25(OH)D during gestation in mothers in the ALSPAC cohort

Serum samples could be from any gestational age and some women had more than one measure of 25(OH)D in pregnancy. The dates of blood sampling were obtained from medical records and used to calculate gestational age at the time of maternal 25(OH)D measurement and adjustment for seasonality. Sine-cosine regression was used to adjust for seasonality, with all measurements (including repeat measures within some women) used in these analyses to obtain a predicted seasonal adjusted mid-third trimester measurements in all women with at least one pregnancy 25(OH)D measure, as described previously[7].

S5 Text: Sensitivity analysis to explore additional sources of invalid instruments

MR-Egger

Like IVW, MR-Egger uses linear regression of the SNP associations with birth weight against the SNP associations with 25(OH)D or calcium, but MR-Egger does not force the intercept through zero, thus relaxing the assumption that the SNP influences birth weight only through the 25(OH)D or calcium (see **Table 1** of main paper)[8]. If a non-zero intercept is observed, this indicates that there may be bias in the fixed effect pooled Wald Ratios and/or IVW instrumental variable estimates due to horizontal pleiotropy. Whilst relaxing the no horizontal pleiotropy assumption and providing an estimate that takes account of non-symmetrical pleiotropy (the slope value), MR-Egger introduces an additional assumption - the Instrument Strength Independent of Direct Effect (INSIDE) assumption. INSIDE assumes that the association of the genetic instrument with the exposure is not correlated with the association of the genetic instrument with the outcome (i.e. the association with outcome that is not via the exposure of interest). In relation to this study the INSIDE assumption is likely to be violated via offspring genotype because of the association of maternal genotype to risk factor and to her offspring genotype[9], and so MR-Egger is unlikely to be a useful approach for testing this source of bias. We use adjustment for offspring genotype to test this (see methods in main paper) and used MR-Egger as a sensitivity analysis to explore possible violation of the exclusion restriction criteria via maternal genetic horizontal pleiotropy. For our MR-Egger analyses we estimated the standard error using a fixed effects model and confidence intervals using a t-distribution.

Weighted-Median Analysis

With weighted-median analysis, the weighted-median instrumental variable of all the SNPs is taken as the causative effect, with each SNP being weighted by its effect on the exposure, thus reducing the effect of single weak instruments (see **Table 1** in main paper)[10]. This method also relaxes the assumption of there being no bias due to asymmetrical horizontal pleiotropy but it assumes that no more than 50% of the combined SNPs weight is from

invalid instruments. This approach will be biased if there is a single horizontal pleiotropic SNP with 50% of the weight or multiple pleiotropic SNPs, each with less than 50% of the weight, but that together are 50% or more of the weight. As with MR-Egger this is likely to be violated by offspring genotype as 50% of maternal alleles will be transferred to the fetus; our fetal genotype adjusted results are the key way of testing for bias via that route[9]. The weighted median analyses were as a sensitivity analysis to explore possible violation of the exclusion restriction criteria via maternal genetic horizontal pleiotropy.

Checking associations of SNPs with observed confounders of gestational 25(OH)D/calcium birth weight associations

To explore the possible association of SNPs with observed confounders, we calculated two weighted allele scores (WAS) from the instrumental variable SNPs for 25(OH)D/calcium and determined the per allele association of these WAS with each confounder. Each SNP was weighted by the magnitude of its effect on the exposure as reported in the original GWAS. The potential confounders we calculated WAS for were; mothers pre-pregnancy BMI, height and smoking (all three in UK Biobank, ALSPAC and EFSOCH), mothers systolic blood pressure and educational attainment (UK Biobank and ALSPAC only), mothers Townsend area of residence deprivation index[11] (UK Biobank and EFSOCH only) and mothers adherence to a Western Diet (UK Biobank only).

Multivariable MR

To adjust for maternal height in the MR analyses of 25(OH)D effects on BW we used genetic instruments (N = 696 SNPs) for from the most recent GWAS of height that had reached genome-wide significance and replicated[12]. To adjust for maternal education in the multivariable MR of the effect of calcium on BW we aimed to use SNPs that were genome-wide significant and replicated from the most recent GWAS of completed years of education

that were genome wide significant and replicated[13]. In both analyses we used the IVW method for the multivariable MR analyses this requires summary data on all of the: exposure SNP associations with exposure, outcome and confounder and confounder SNP associations with confounder outcome and exposure. In the analyses of calcium we were unable to do this because data were only provided for the genome-wide significant hits and not the whole genome which meant that we could not find confounder (maternal education) SNP associations with calcium for all of the education hits. We therefore did a partial multivariable MR to adjust calcium-BW effects for maternal education.

S1 Table: Characteristics of the genome-wide association studies of 25(OH)D

Study	Trait	Population	No of Discovery cohorts	No of Discovery participants	No of Recovery cohorts	No of Recovery participants	N (total)	N(%) of participants that were female
Manousaki et al 2017[14]	25[OH]D	European	2	2,619	17	39,655	42,274	39.5
Jiang et al 2018[15]	25[OH]D	European	31	79,366	2	42,757	122,123	NA
O'Seaghdha et al 2013[16]	Calcium	European	19	39,400	11	21,875	61,275	0

NA: data on proportion of males and females not provided

S2 Table: Details of SNPs used in our Mendelian Randomisation analyses

Trait	SNP	Nearest/Nearby gene	Trait raising allele	Trait lowering allele	Trait raising allele frequency (GWAS reported)	Difference in mean 25(OH)D or calcium (95% CI) per allele	Units of change in 25(OH)D or calcium per allele and GWAS used to obtain these results
Vitamin D (synthesis)	rs10741657	*CYP2R1*	A	G	0.4	0.031 (0.027 to 0.035)	Log nmol/l (Jiang et al (2018) Nature Communications)[15]
Vitamin D (synthesis)	rs117913124	*CYP2R1*	G	A	0.975	0.21 (0.19 to 0.23)*	Log nmol/l (Manousaki et al (2017) The American Journal of Human Genetics) [14]
Vitamin D (synthesis)	rs12785878	*DHCR7*	T	G	0.75	0.036 (0.032 to 0.04)	Log nmol/l (Jiang et al (2018) Nature Communications)[15]
Vitamin D (metabolism)	rs3755967	*GC*	C	T	0.72	0.089 (0.084 to 0.094)	Log nmol/l (Jiang et al (2018) Nature Communications)[15]
Vitamin D (metabolism)	rs17216707	*CYP24A1*	T	C	0.79	0.026 (0.021 to 0.031)	Log nmol/l (Jiang et al (2018) Nature Communications)[15]
Vitamin D	rs10745742	*AMDHD1*	T	C	0.41	0.017 (0.013 to 0.021)	Log nmol/l (Jiang et al (2018) Nature Communications)[15]

Vitamin D	rs8018720	*SEC23A*	G	C	0.27	0.017 (0.012 to 0.022)	Log nmol/l (Jiang et al (2018) Nature Communications)[15]
Calcium	rs1801725	*CASR*	T	G	0.15	0.071 (0.063 to 0.079)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]
Calcium	rs1550532	*DGKD*	C	G	0.31	0.018 (0.012 to 0.024)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]
Calcium	rs780094	*GCKR*	T	C	0.41	0.017 (0.011 to 0.023)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]
Calcium	rs10491003	*GATA3*	T	C	0.09	0.027 (0.017 to 0.037)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]
Calcium	rs7481584	*CARS*	G	A	0.71	0.018 (0.012 to 0.024)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]
Calcium	rs7336933	*DGKH; KIAA0564*	G	A	0.85	0.022 (0.014 to 0.03)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]
Calcium	rs1570669	*CYP24A1*	G	A	0.33	0.018 (0.012 to 0.024)	Mg/dl (O'Seaghdha et al (2013) PLOS Genetics)[16]

*The reported value in Manousaki et al[14] was 0.43 (0.39 to 0.47) standard deviations of 25(OH)D in log nmol/L, to get the value in log nmol/L we multiplied by 0.487, the standard deviation for 25(OH)D levels in ALSPAC in log nmol/L

S3 Table: Studies used to calculate the RCT instrumental variable effect of 25(OH)D on birth weight

Studies	Number of participants in the study	Mean Difference in birth weight between supplementation and placebo group, in g	Mean Difference in 25(OH)D levels between supplementation and placebo group, in nmol/l
Mutlu (L) 2014[17]	59	24 (-379.48 to 427.48)	2.75 (-8.93 to 14.42)
Yu (H) 2009[18]	120	22 (-240.1 to 284.1)	5.67 (1.28 to 10.06)
Khan (2016)[19]	85	-180 (-488.76 to 128.76)	9.98 (2.46 to 17.51)
Vaziri (2016)[20]	127	-58 (-203.82 to 87.82)	15.03 (8.1 to 21.95)
Mallet (L) (1986)[21]	56	-90 (-339.46 to 159.46)	15.9 (11.75 to 20.05)
Mallet (H) (1986)[21]	50	-250 (-512.22 to 12.22)	16.6 (13.11 to 20.09)
Dawodu (L) (2013)[22]	129	91 (-102.45 to 284.45)	16.67 (5.13 to 28.22)
Yu (L) (2009)[18]	120	53 (-214.38 to 320.38)	18.67 (9.64 to 27.69)
Mutlu (H) (2014)[17]	60	-60 (-459.98 to 339.38)	18.97 (9.73 to 28.21)
Hollis (L) (2011)[23]	333	138.3 (-67.38 to 343.98)	19.4 (8.04 to 30.76)
Sahoo (L) (2016)[24]	39	110 (-278.99 to 498.99)	22.8 (8.21 to 37.39)
Thiele (2016)	13	-102 (-638.05 to 434.05)	23.14 (15.41 to 30.87)
Mojibian (2015)[25]	500	-36.85 (-128.29 to 54.59)	26.71 (17.11 to 36.3)
Yap (2014)[26]	179	70 (-135.3 to 275.3)	29.95 (22.12 to 37.79)
Zerofsky (2014)[27]	57	289 (10.78 to 567.22)	30.4 (19.91 to 40.89)
Litonjua (2016)[28]	440	-14.6 (-92.94 to 63.74)	31.2 (26.46 to 35.94)
Hollis (H) (2011)[23]	335	62.8 (-145.17 to 270.77)	32.1 (20.03 to 44.17)

Valizadeh (2016)[29]	96	217 (-14.9 to 448.9)	32.7 (19.63 to 45.76)
Sablok (2015)[30]	180	200 (88.39 to 311.61)	33.89 (12.31 to 55.47)
Sahoo (H) (2016)[24]	29	0 (-350.15 to 350.15)	35.3 (20.09 to 50.51)
Dawodu (H) (2013)[22]	127	2 (-217.22 to 221.22)	41.56 (29.15 to 53.97)
Asemi (b) (2013)[31]	54	120.5 (-153.57 to 394.57)	45 (18.35 to 71.65)
Grant (L) (2014)[32]	174	28.33 (-152.21 to 208.88)	45.76 (33.84 to 57.68)
Grant (H) (2014)[32]	173	88.33 (-87.01 to 263.68)	48.26 (34.49 to 62.02)
Abotorabi (2017)[33]	110	33.7 (-139.04 to 206.44)	48.6 (39.91 to 57.29)
Hashemipour (2013)[34]	160	170.2 (42.48 to 297.92)	79.62 (71.08 to 88.16)
Roth (2013)[35]	160	14 (-138.82 to 166.82)	96 (87.4 to 104.6)
Brooke (1980)[36]	126	123 (-50.29 to 296.29)	151.8 (126.74 to 176.86)
Karamali (2015)[37]	60	172.6 (-42.78 to 387.98)	43.78 (39.6 to 47.96)
Sabet (2012)[38]	50	45 (-136.32 to 226.32)	80 (46.73 to 113.26)
Cooper (2016)[39]	1134	-37 (-104.21 to 30.21)	24.5 (21.7to27.3)

The RCTs used in the analyses of the effect of gestational circulating 25(OH)D on birth weight were identified from the systematic review by Roth et al 2017[40]

S4 Table: Studies used to calculate the RCT instrumental variable effect of calcium on birth weight

Studies	Number of participants in the study	Mean Difference in birth weight between supplementation and placebo group, in g	Mean Difference in calcium levels between supplementation and placebo group, in mg/dl
Boggess (1997)[41]	18	82 (-97.3 to 261.3)	0.1 (-6.262 to 6.462)
Chan (2006)[42]	41	15 (-89.87 to 119.87)	0.1 (-0.51 to 0.71)
Lopez-Jaramillo (1989)[43]	92	265 (142.5 to 287.5)	0.16 (-0.12 to 0.44)
Lopez-Jaramillo (1997)[44]	260	110 (73.44 to 146.56)	0.28 (0.28 to 0.28)
Belizan (1983) (1g supplement)[45]	16	-354.000 (-751.35 to 43.35)	0.42 (-1.97 to 2.81)
Belizan (1983) (2g supplement)[45]	16	42.000 (-268.82 to 352.82)	0.94 (-2.14 to 4.02)
Wanchu 2001[46]	100	100.000 (-77.48 to 277.48)	0.3 (-0.39 to 0.99)

The RCTs used in the analyses of the effect of gestational circulating 25(OH)D on birth weight were identified from the systematic review by Buppasiri et al 2015[47]

S5 Table:SNP effects on first child birth weight in all studies

SNP	Study	SNP-outcome effect (g)
rs10741657	UK Biobank (N=190,406)	1.517 (-1.567 to 4.601)
	ALSPAC (N=4,576)	12.076 (-6.313 to 30.464)
	EFSOCH (N=647)	-7.120 (-54.209 to 39.968)
rs117913124	UK Biobank (N=190,406)	-1.121(-10.34 to 8.097)
	ALSPAC (N=4,576)	0.244 (-55.124 to 55.613)
	EFSOCH (N=647)	19.734 (-123.241 to 162.71)
rs12785878	UK Biobank (N=190,406)	2.030 (-1.682 to 5.742)
	ALSPAC (N=4,576)	15.855 (-5.217 to 36.927)
	EFSOCH (N=647)	-0.542 (-57.256 to 56.173)
rs3755967	UK Biobank (N=190,406)	-0.756 (-4.09 to 2.578)
	ALSPAC (N=4,576)	9.447 (-10.41 to 29.303)
	EFSOCH (N=647)	34.727 (-17.749 to 87.202)
rs17216707	UK Biobank (N=190,406)	1.943 (-2.001 to 5.888)
	ALSPAC (N=4,576)	0.926 (-22.32 to 24.173)
	EFSOCH (N=647)	2.150 (-63.878 to 68.177)
rs10745742	UK Biobank (N=190,406)	-1.813 (-4.951 to 1.324)
	ALSPAC (N=4,576)	-1.352 (-20.246 to 17.543)
	EFSOCH (N=647)	-34.556 (-82.902 to 13.789)
rs8018720	UK Biobank (N=190,406)	-1.862 (-5.835 to 2.111)
	ALSPAC (N=4,576)	6.977 (-16.75 to 30.704)
	EFSOCH (N=647)	13.136 (-50.613 to 76.885)
rs1801725	UK Biobank (N=190,406)	1.349 (-3.166 to 5.865)
	ALSPAC (N=4,576)	31.759 (4.884 to 58.634)
	EFSOCH (N=647)	-18.180 (-87.642 to 51.282)
rs1550532	UK Biobank (N=190,406)	-2.579 (-5.832 to 0.674)
	ALSPAC (N=4,576)	-6.095 (-25.7 to 13.511)
	EFSOCH (N=647)	-1.471 (-53.177 to 50.236)
rs780094	UK Biobank (N=190,406)	-5.379 (-8.495 to -2.263)

	ALSPAC (N=4,576)	-1.747 (-20.415 to 16.921)
	EFSOCH (N=647)	-24.770 (-70.675 to 21.135)
rs10491003	UK Biobank (N=190,406)	1.169 (-4.065 to 6.403)
	ALSPAC (N=4,576)	-0.579 (-32.680 to 31.521)
	EFSOCH (N=647)	-19.229 (-100.591 to 62.133)
rs7481584	UK Biobank (N=190,406)	-2.195 (-5.553 to 1.164)
	ALSPAC (N=4,576)	-4.468 (-24.868 to 15.932)
	EFSOCH (N=647)	-1.612 (-56.211 to 52.987)
rs7336933	UK Biobank (N=190,406)	-3.252 (-7.474 to 0.97)
	ALSPAC (N=4,576)	6.193 (-19.201 to 31.586)
	EFSOCH (N=647)	-42.09 (-108.322 to 24.142)
rs1570669	UK Biobank (N=190,406)	-0.573 (-3.781 to 2.636)
	ALSPAC (N=4,576)	-9.767 (-28.881 to 9.347)
	EFSOCH (N=647)	21.217 (-28.934 to 71.367)

S6 Table: SNP effects on own birth weight in UK Biobank (N=215,444)

SNP	SNP-outcome effect (g)
rs10741657	4.083 (1.178 to 6.987)
rs117913124	-3.97 (-12.703 to 4.763)
rs12785878	3.349 (-0.134 to 6.831)
rs3755967	0.652 (-2.487 to 3.792)
rs17216707	4.041 (0.339 to 7.742)
rs10745742	-0.533 (-3.479 to 2.412)
rs8018720	-1.492 (-5.232 to 2.249)
rs1801725	-6.466 (-10.715 to -2.217)
rs1550532	-5.091 (-8.151 to -2.03)
rs780094	-1.948 (-4.878 to 0.983)
rs10491003	2.010 (-2.932 to 6.951)
rs7481584	1.236 (-1.923 to 4.396)
rs7336933	0.208 (-3.769 to 4.186)
rs1570669	3.407 (0.392 to 6.423)

S7 Table: SNP effects on fetal adjusted birth weight in ALSPAC and EFSOCH

SNP	Study	SNP-outcome effect (g)
rs10741657	ALSPAC (N=4,576)	12.325 (-8.705 to 33.355)
	EFSOCH (N=647)	-21.514 (-76.659 to 33.631)
rs117913124	ALSPAC (N=4,576)	9.165 (-56.077 to 74.407)
	EFSOCH (N=647)	11.226 (-147.894 to 170.345)
rs12785878	ALSPAC (N=4,576)	27.337 (3.041 to 51.633)
	EFSOCH (N=647)	-15.656 (-80.016 to 48.704)
rs3755967	ALSPAC (N=4,576)	13.299 (-9.578 to 36.176)
	EFSOCH (N=647)	42.838 (-18.736 to 104.412)
rs17216707	ALSPAC (N=4,576)	-0.508 (-27.622 to 26.607)
	EFSOCH (N=647)	-12.660 (-87.102 to 61.782)
rs10745742	ALSPAC (N=4,576)	-3.128 (-24.790 to 18.533)
	EFSOCH (N=647)	-59.398 (-116.456 to -2.34)
rs8018720	ALSPAC (N=4,576)	-3.236 (-30.492 to 24.019)
	EFSOCH (N=647)	20.294 (-53.447 to 94.034)
rs1801725	ALSPAC (N=4,576)	31.476 (0.706 to 62.246)
	EFSOCH (N=647)	-43.012 (-120.582 to 34.558)
rs1550532	ALSPAC (N=4,576)	5.037 (-17.553 to 27.627)
	EFSOCH (N=647)	-16.937 (-77.309 to 43.435)
rs780094	ALSPAC (N=4,576)	8.070 (-13.375 to 29.515)
	EFSOCH (N=647)	-31.69 (-85.520 to 22.139)
rs10491003	ALSPAC (N=4,576)	-6.140 (-42.415 to 30.134)
	EFSOCH (N=647)	-48.253 (-139.743 to 43.236)
rs7481584	ALSPAC (N=4,576)	-2.332 (-25.799 to 21.135)
	EFSOCH (N=647)	-4.990 (-67.296 to 57.317)
rs7336933	ALSPAC (N=4,576)	2.363 (-26.832 to 31.558)
	EFSOCH (N=647)	-17.501 (-94.267 to 59.265)
rs1570669	ALSPAC (N=4,576)	-17.949 (-39.990 to 4.092)
	EFSOCH (N=647)	10.717 (-47.005 to 68.439)

S8 Table: Risk of Bias in studies included in IV of RCT analyses of Vitamin D supplementation

Study	Number randomised	Loss to follow-up (%)[a]	Placebo control	Intention to treat analysis[a]	Risk of Bias[b]						
					RSG	AC	BP	BO	IOD	SR	Other
Abotorabi (2017)[33]	110	23	No	Unclear	Low	Unclear	High	Unclear	Low	High	Low
Asemi (2013)[31]	54	11	Yes	Yes	Low	Low	Low	Low	Low	Low	Low
Brooke (1980)[36]	130 analysed	Unclear	Yes	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
Cooper (2016)[39]	1134	15	No	Low	Low	Low	Low	Low	Low	Low	Low
Dawodu (L) (2013)[22]	129	17	No	No	Low	Low	Low	Low	High	High	Low
Dawodu (H) (2013)[22]	127	13	No	No	Low	Low	Low	Low	High	High	Low
Grant (L) (2014)[32]	174	3	Yes	Unclear	Low	Low	Low	Low	Low	Low	Low
Grant (H) (2014)[32]	173	3	Yes	Unclear	Low	Low	Low	Low	Low	Low	Low
Hashemipour (2013)[34]	130	6	No	No	Low	Low	High	High	Low	Low	Low
Hollis (L) (2011)[23]	333	30	Yes	No	High	Low	Low	Low	Low	Low	Low
Hollis (H) (2011)[23]	335	32	Yes	No	High	Low	Low	Low	Low	Low	Low
Karamali (2015)[37]	30 analysed	Unclear	Yes	Unclear	Low	Low	Low	Low	Low	Low	Low

Khan (2016)[19]	85	Unclear	Yes	Unclear	Unclear	Low	Low	Low	Unclear	Low	Low
Litonjua (2016)[28]	881	8	No	No	Low	Unclear	Low	Low	Low	Low	Low
Mallet (L) (1986)[21][c]	Unclear (36 analysed)	Unclear	Yes	Unclear	Low	Unclear	High	Low	Low	Low	Low
Mallet (H) (1986)[21][c]	Unclear (30 analysed)	Unclear	Yes	Unclear	Low	Unclear	High	Low	Low	Low	Low
Mojibian (2015)[25]	500	22	No	No	Low	Low	High	High	High	Low	Low
Mutlu (L) 2014[17]	59	24	No	No	Unclear	Unclear	High	High	Low	Low	Low
Mutlu (H) (2014)[17]	60	27	No	No	Unclear	Unclear	High	High	Low	Low	Low
Roth (2013)[35]	160	8	Yes	No	Low	Low	Low	Low	Low	Low	Low
Sabet (2012)[38]	50 analysed	Unclear	Yes	Unclear	Unclear	Unclear	Low	Low	Low	Low	Low
Sablok (2015)[30]	180	8	No	No	Low	Unclear	High	Unclear	Unclear	High	Low
Sahoo (L) (2016)[24]	200	85[d]	Yes	No	Low	Low	Low	Low	High	Low	Low
Sahoo (H) (2016)[24]	200	80[d]	No	No	Low	Low	Low	Low	High	Low	Low
Thiele (2016)[48]	16	19	Yes	Yes	Unclear	Unclear	Low	Low	Unclear	Unclear	Low
Yap (2014)[26]	169	6	No	No	High	High	Low	Low	Low	High	Low

Valizadeh (2016)[29]	96	6	No	Unclear	Unclear	Low	High	High	Low	Low	Low
Vaziri (2016)[20]	153	17%	No	No	Unclear	Unclear	Low	Low	Low	High	Low
Yu (L) (2009)[18]	120	1	No	Unclear	Low	High	High	High	Low	Low	Low
Yu (H) 2009[18]	120	1	No	Unclear	Low	High	High	High	Low	Low	Low
Zerofsky (2014)[27]	57	14	Yes	No	Low	Low	Low	Low	Low	Low	Low

Note there are 30 rows in this table which reflects the 30 instrumental variable estimates from the 24 RCTs that were included in these analyses; two IV estimates were obtained from six trials in which participants were randomised to one of three groups: low dose vitamin D (L), high dose vitamin D (H) or control

[a] All entries relate to analyses of birth weight (birth weight is often not the primary outcome in these trials and the results may be different for the primary outcomes)

[b] Each of the seven categories were categorised by reviewers as low, medium, or high risk of bias or unclear. RSG: Random Sequence Generation; AC: Allocation Concealment; BP: Blinding of personnel/participants (performance bias); BO: Blinding of outcome assessment (detection bias); IOD: Incomplete outcome data (attrition bias); SR: Selective Reporting; Other: other sources of bias.

[c] For this study we were only able to access the abstracts and not the full papers

[d] This study was primarily concerned with outcomes at 12-16 months and over 80% were lost to follow-up by this age (47% had been lost to follow-up at birth but differences in BW between randomised groups was only presented in those included in the 12-16 months follow-up).

S9 Table: Risk of Bias in studies included in IV of RCT analyses of Calcium supplementation

Study	Number randomised	Loss to follow-up (%)	Placebo control	Intention to treat analysis	Risk of Bias*						
					RSG	AC	BP	BO	IOD	SR	Other
Bogges 1997[41]	23	22%	Yes	No	low	low	low	low	unclear	low	low
Belizan 1983[45]	36	Unclear '0 missing data'	Yes	Yes	unclear	unclear	low	low	low	low	low
Chan 2006[42]**	72	8%	No	No	low	low	high	high	low	unclear	low
Lopez-Jaramillo 1989[43]	106	13%	Yes	Yes	low	low	low	low	unclear	unclear	low
Lopez-Jaramillo 1997[44]	274	5%	Yes	No	low	low	low	low	low	low	low
Wanchu 2001[46]	120	17%	No	No	unclear	unclear	high	high	high	unclear	low

* Each of the seven categories were categorised by reviewers as low, medium, or high risk of bias or unclear. RSG: Random Sequence Generation; AC: Allocation Concealment; BP: Blinding of personnel/participants (performance bias); BO: Blinding of outcome assessment (detection bias); IOD: Incomplete outcome data (attrition bias); SR: Selective Reporting; Other: other sources of bias

** Chan participants were randomised to control or one of two intervention groups: orange juice with calcium fortification or increased diary intake (only the comparison of orange just with calcium fortification to control group was used here); the other three studies compared calcium supplementation tablets to placebo or no supplementation (control groups)

S10 Table: Associations between weighted-allele-scores and potential confounders

	Study	Difference in mean or odds ratio (95% CI) per unit increase in weighted allele score (WAS)	
		25(OH)D	Calcium
Maternal BMI (kg/m^2)*	UK Biobank (N = 243,797)[c,e]	0.001 (-0.007 to 0.009)	0.001 (-0.002 to 0.005)
	ALSPAC (N =6,544)	-0.020 (-0.073 to 0.034)	-0.008 (-0.030 to 0.014)
	EFSOCH (N =844)	0.102 (-0.042 to 0.247)	0.031 (-0.030 to 0.092)
Maternal Height (m)*	UK Biobank (N = 244,363)[d,e]	-0.010 (-0.017 to -0.003)	-0.002 (-0.005 to 0.001)
	ALSPAC (N =6,862)	0.020 (-0.032 to 0.073)	-0.004 (-0.026 to 0.018)
	EFSOCH (N =930)	0.163 (0.024 to 0.302)	0.026 (-0.032 to 0.084)
Maternal Systolic Blood Pressure (mmHg)*	UK Biobank (N = 244,183)[e]	-0.002 (-0.009 to 0.006)	-0.001 (-0.004 to 0.002)
	ALSPAC (N =1,451)	-0.033 (-0.150 to 0.084)	-0.033 (-0.080 to 0.014)
	EFSOCH (N =NA)	NA	NA
Maternal Townsend area deprivation*[a]	UK Biobank (N = 244,564)	0.002 (-0.006 to 0.010)	0.004 (0.000 to 0.007)
	ALSPAC (N =NA)	NA	NA
	EFSOCH (N =933)	-0.196 (-0.336 to -0.055)	-0.016 (-0.075 to 0.043)
Education (odds ratio of university degree yes or no)	UK Biobank (N = 238,261)[e]	0.997 (0.979 to 1.014)	0.987 (0.980 to 0.995)
	ALSPAC (N =6,956)	1.032 (0.876 to 1.188)	0.955 (0.897 to 1.012)
	EFSOCH (N =NA)	NA	NA
Maternal smoking (odds ratio of current smoker vs non-smoker)	UK Biobank (N = 160,043)[e]	0.983 (0.951 to 1.015)	1.008 (0.994 to 1.022)
	ALSPAC (N =7,237)	0.990 (0.859 to 1.122)	1.007 (0.950 to 1.065)
	EFSOCH (N =928)	1.233 (0.549 to 1.917)	1.001 (0.831 to 1.172)
Western Diet[b]	UK Biobank (N = 355,829)[e]	-0.001 (-0.008 to 0.006)	0.001 (-0.002 to 0.004)
	ALSPAC (N =NA)	NA	NA
	EFSOCH (N =NA)	NA	NA

*The values given are z-scores/single inverse normalized. a) A score that takes values from the census of an area (namely percentage of households without a motor vehicle, percentage of households with more than one person per room, percentage of households not owner-

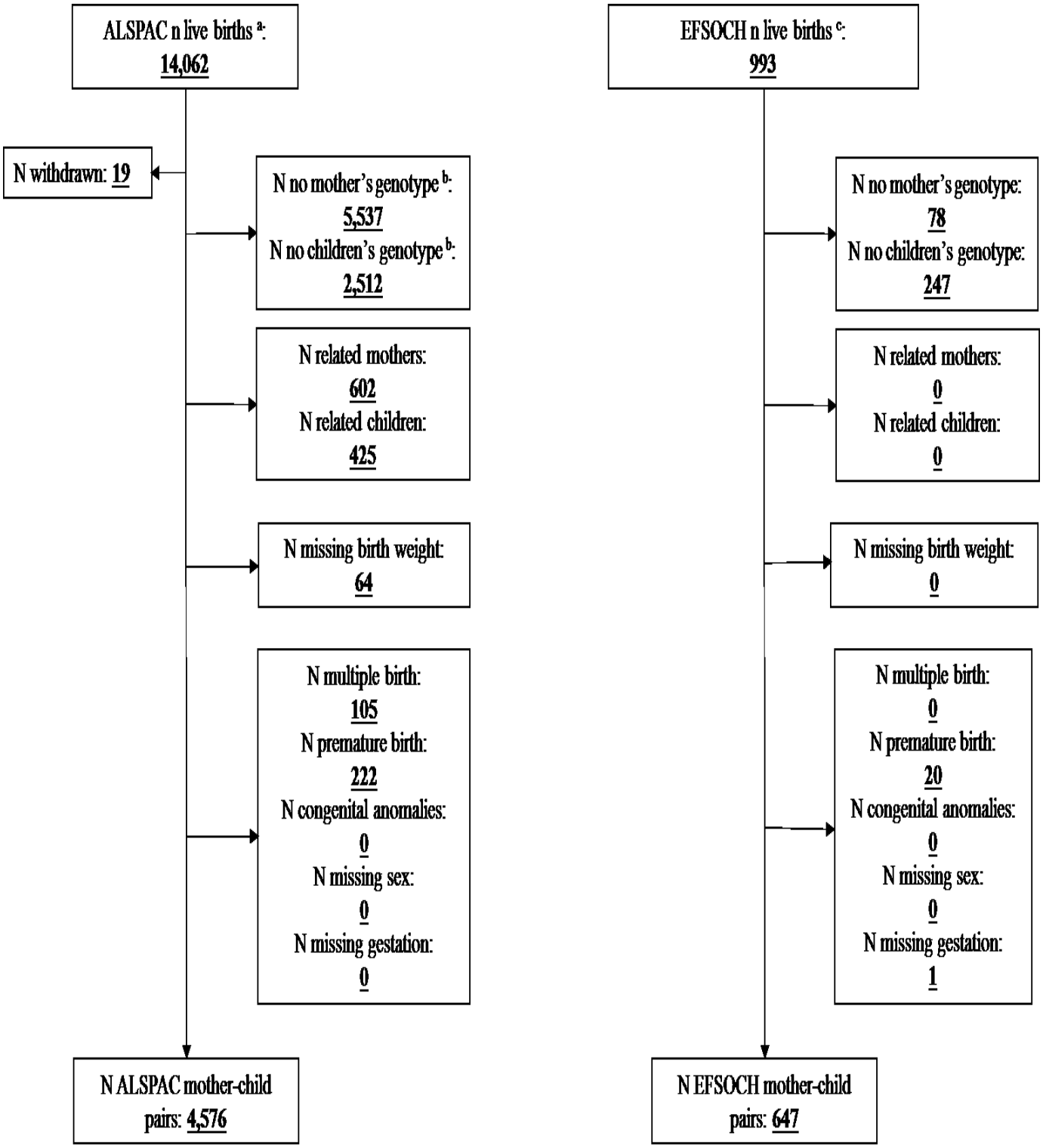
occupied and percentage of residents who are unemployed), converts them to z-scores, then adds the values up, with a greater value meaning greater deprivation. b) Western Diet is a principal component of variation in reported diet in UK Biobank. c) The UK Biobank female BMI variable excluded those with a BMI <15 and those that were pregnant, the variable then being adjusted for age, assessment centre and five principal components, with the residuals being extracted and inverse-normalized. d) The UK Biobank female Height variable was adjusted for age, assessment centre and five principal components, with the residuals being extracted and inverse-normalized. e) All UK Biobank variables were adjusted for five principal components

S11 Table: Multivariable MR for 25(OH)D and calcium effect on birth weight in UK Biobank (adjusting for height effects)

MR Model	Exposure-outcome effect (g)
IVW for 25(OH)D (main result)	-0.03 (-3.08 to 3.03)
IVW leaving rs117913124 out[a]	0.22 (-3.74 to 4.17)
Multivariable model IVW for 25(OH)D with exposure and height SNPs adjusted for height [b]	-0.60 (-4.79 to 1.95)
IVW for calcium (main result)	-20 (-50 to 11)
Partial multivariable model for calcium [c]	-45 (-97 to 7)

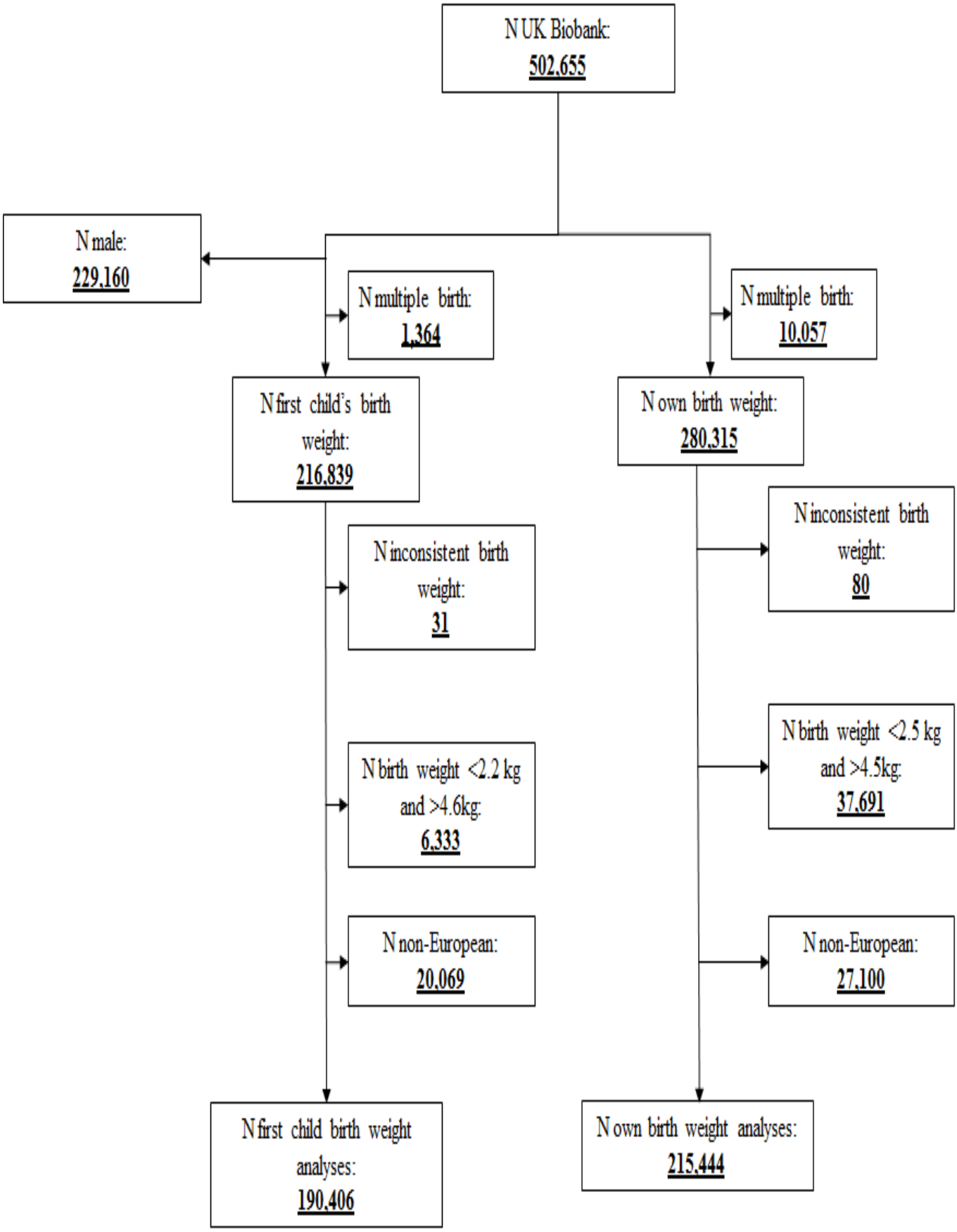
[a] There was no summary data for rs117913124 (one of the 25(OH)D genetic instruments), or any proxies, in the GWAS of height used for this multivariable MR analysis[12] therefore we have included in this table both the main unadjusted IVW result and also the result with rs117913124 left out so that we can compare the multivariable IVW adjusted for height to both the main results and one with rs117913124 left out (as this has to be left out in the multivariable MR analyses) [b] Multivariable IVW MR analyses in which we adjust the 25(OH)D-BW effect for the potential confounding effect of height. [c] In these analyses we were only able to adjust for maternal education by including the summary difference in mean education for each calcium (genetic instrument) SNP along with their difference in mean calcium.

S1 Figure: Flow diagram of participant inclusion for ALSPAC and EFSOCH

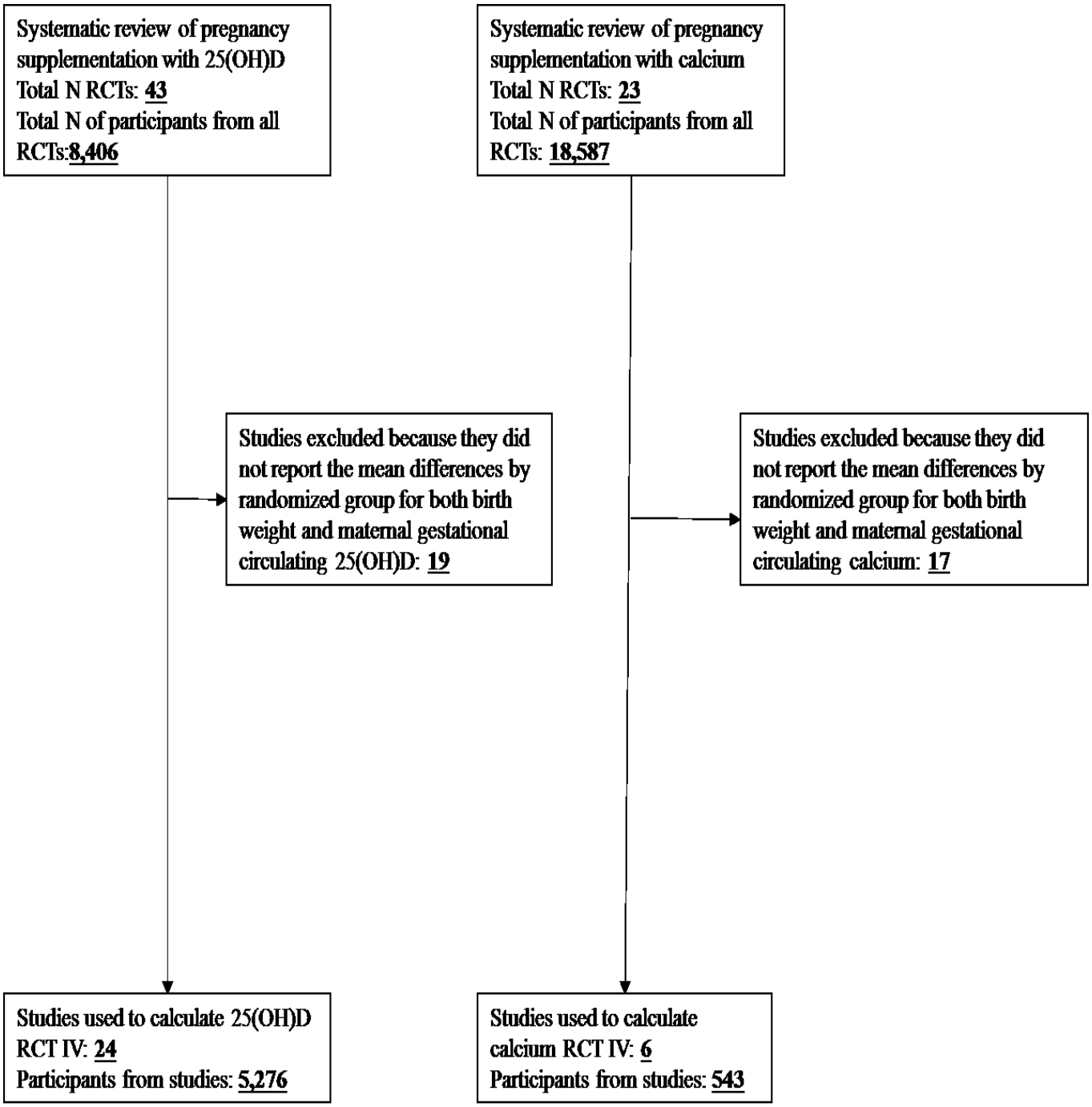


a) All participants were recruited as part of the core phase and were born alive.
b) All genotyped participants were White European.
c) All participants were born alive; they were also all White European (recruited at onset) and related individuals and twins were pre-excluded.

S2 Figure: Flow diagram for participant inclusion in UK Biobank

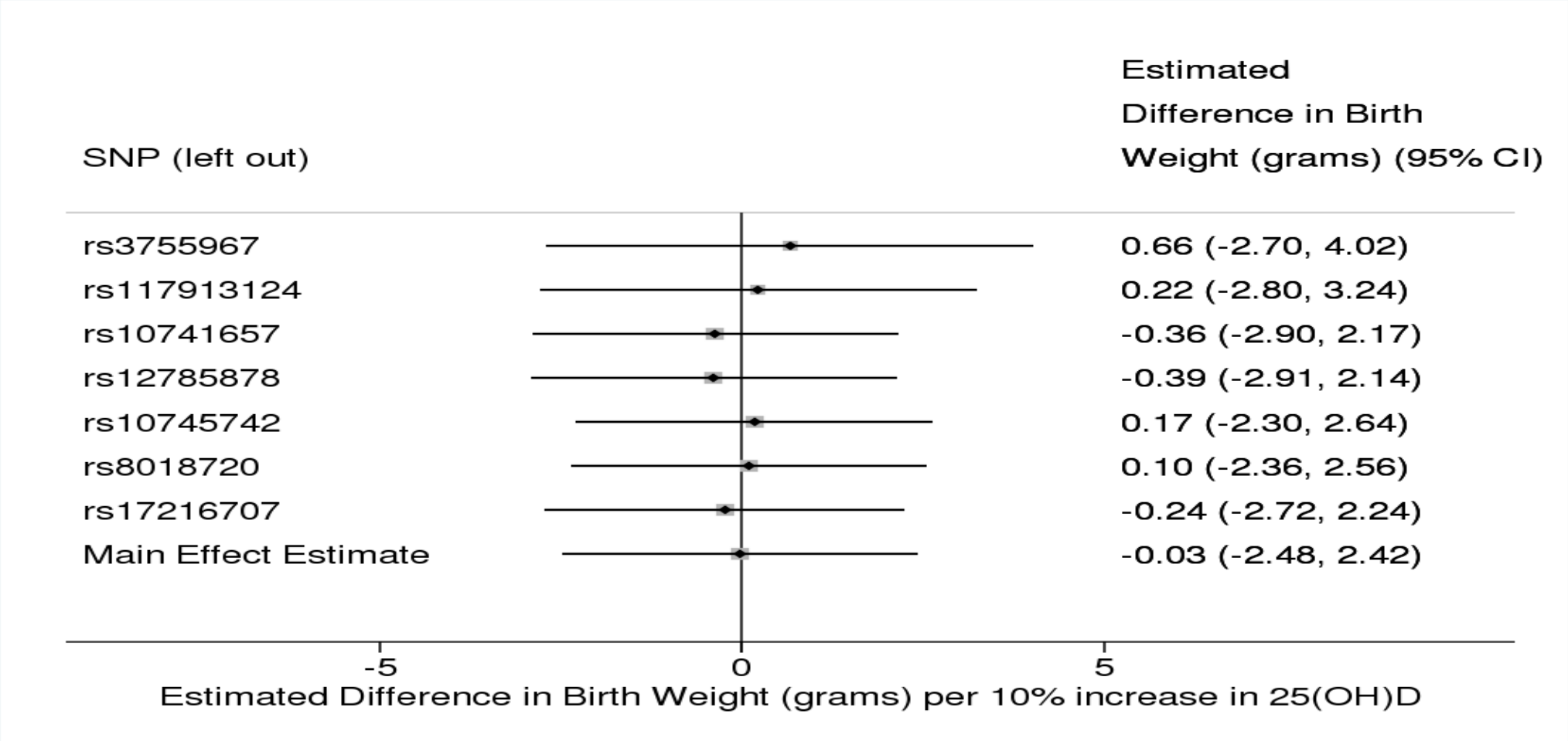


S3 Figure: Flow diagram for inclusion of trials in the instrumental variables applied to RCTs



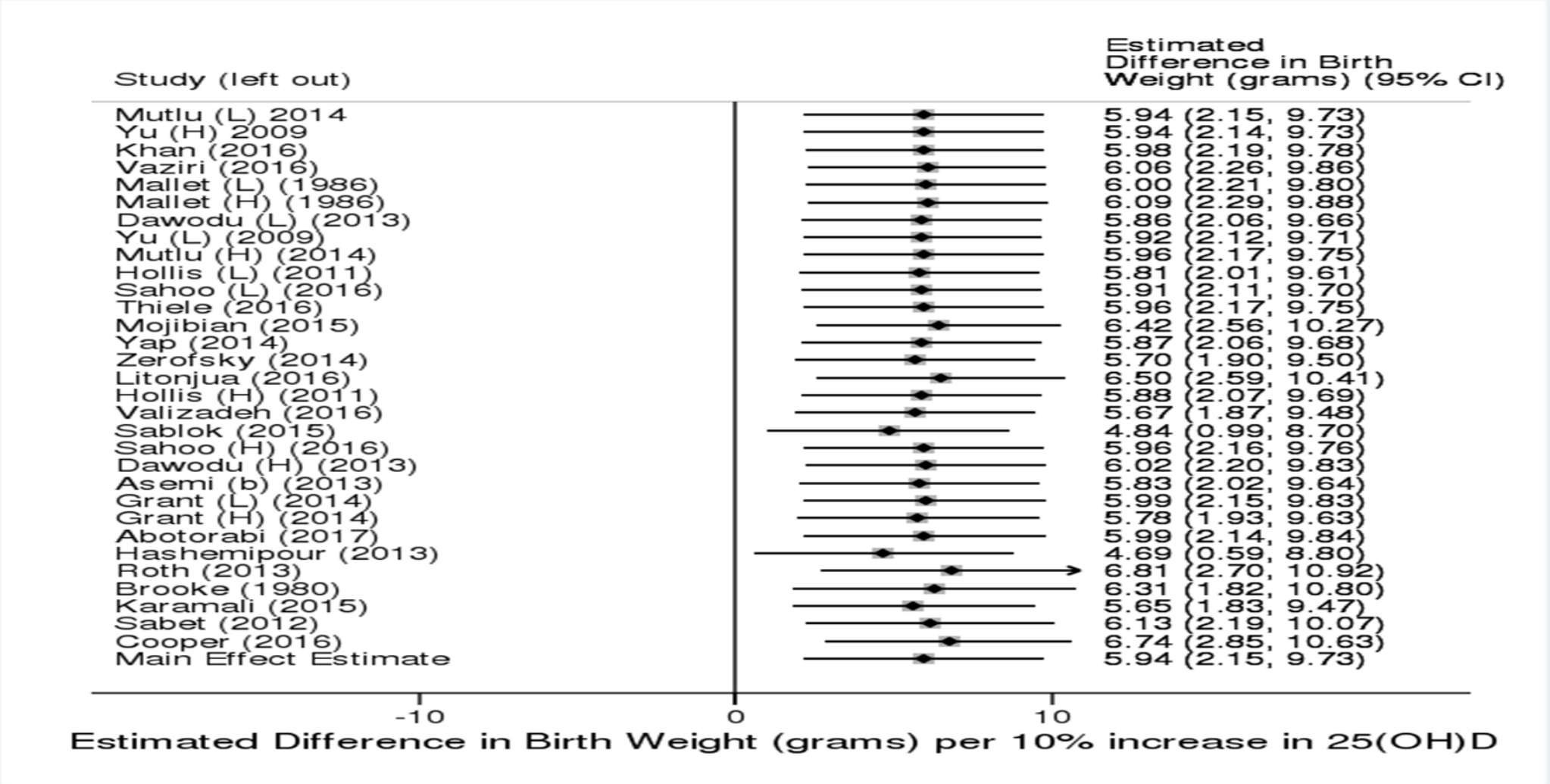
Studies for 25(OH)D were taken from Roth et al 2017[40] and studies for calcium were taken from Buppasiri et al 2015[47].

S4 Figure: Leave-One-Out Analysis for effect of maternal gestational circulating 25(OH)D on birth weight Mendelian randomisation Wald ratio estimate in UK Biobank



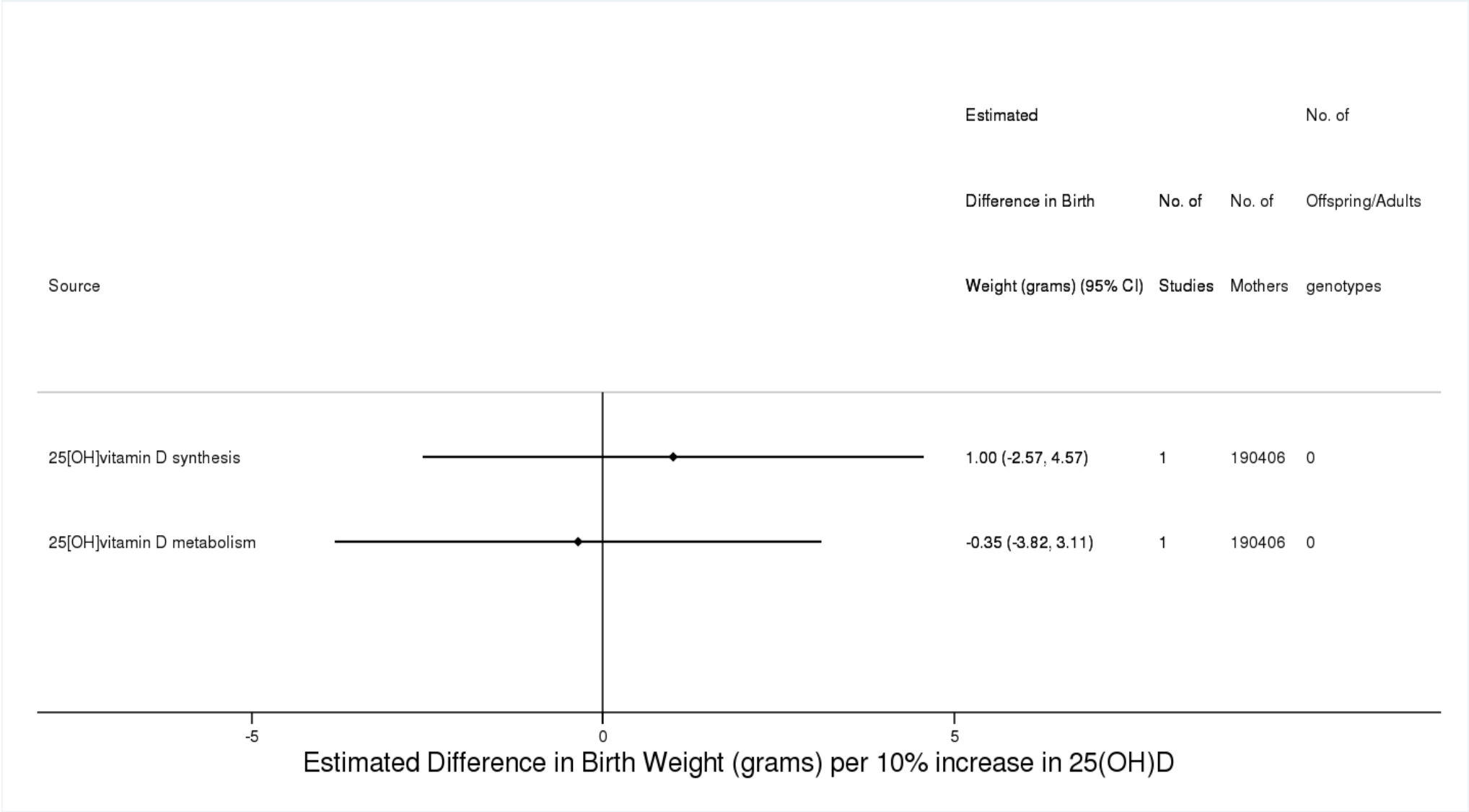
SNPs were taken from Manousaki et al 2017[14] and Jiang et al 2018[15].

S5 Figure: Leave-One-Out Analysis for effect of 25(OH)D on birth weight RCT instrumental variable Wald ratio estimate

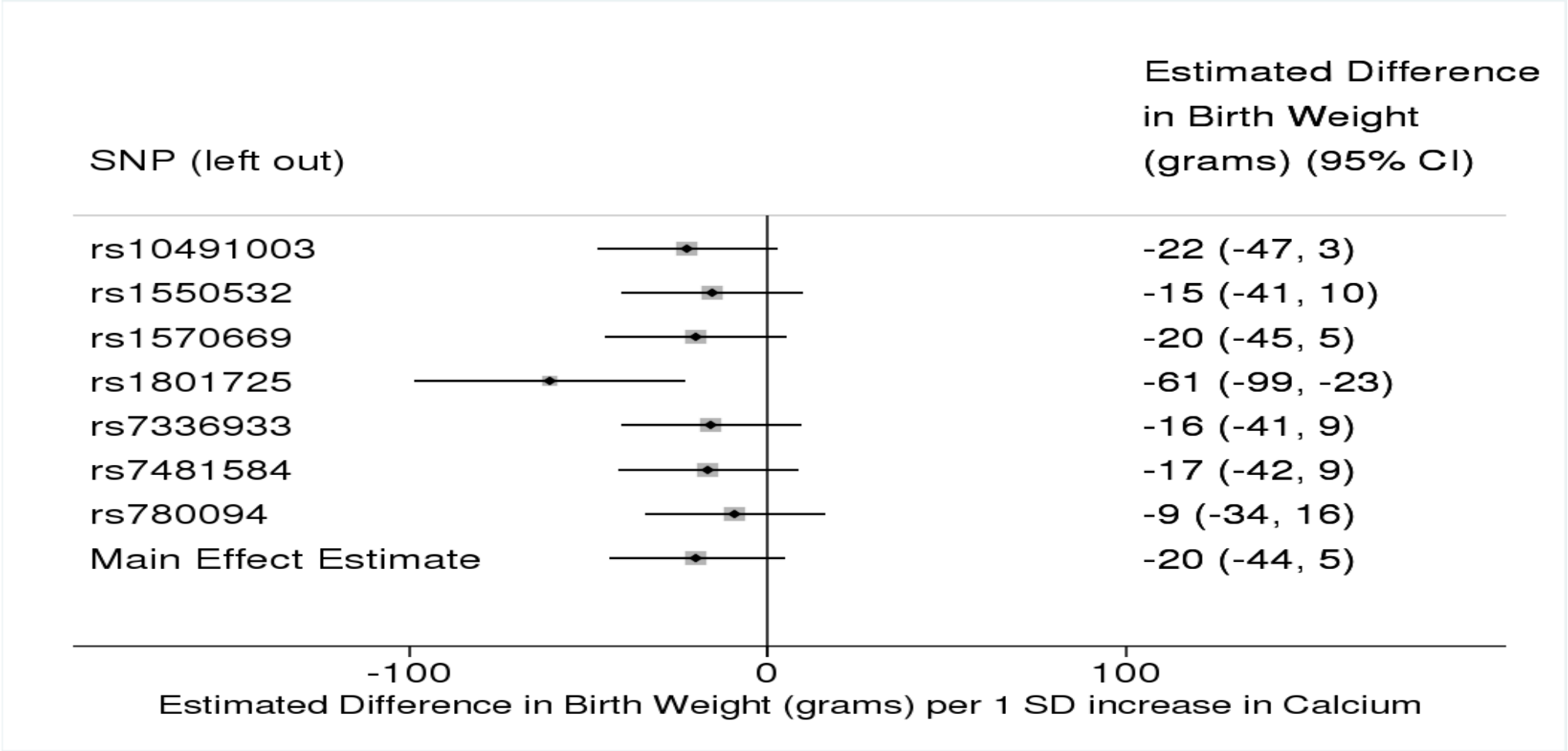


Studies were taken from Roth et al 2017[40].

S6 Figure: Mendelian randomisation effect estimates for maternal 25(OH)D synthesis and metabolism on birth weight in UK Biobank

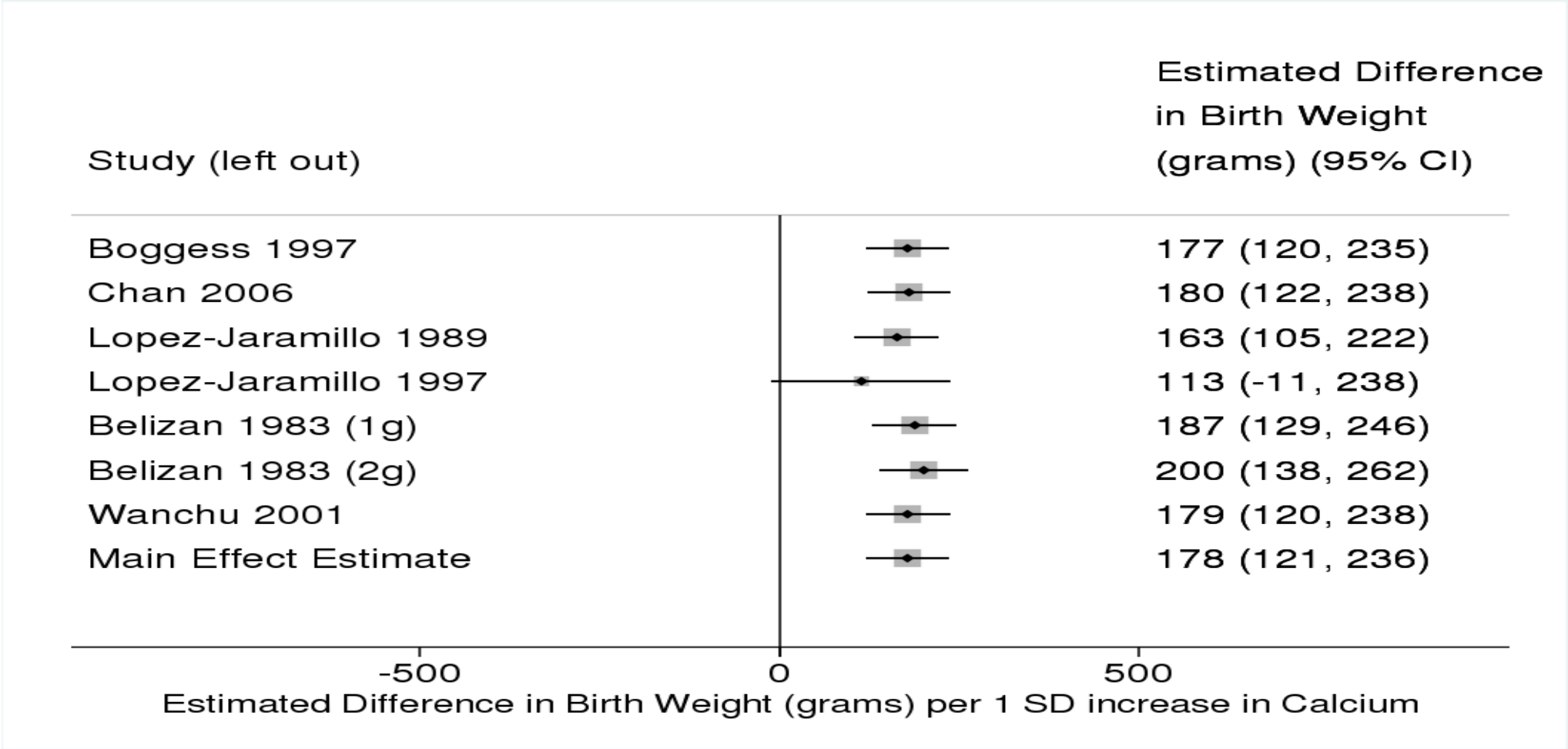


S7 Figure: Leave-One-Out Analysis for effect of maternal gestational circulating calcium on birth weight Mendelian randomisation Wald ratio estimate in UK Biobank



SNPs were taken from O'Seaghdha et al 2013[16]

S8 Figure: Leave-One-Out Analysis for effect of maternal gestational circulating calcium RCT instrumental variable Wald ratio estimate



Studies were taken from Buppasiri et al 2015[47].

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