Integrating multiple lines of evidence to assess the effects of maternal BMI on pregnancy and perinatal outcomes

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Abstract

Background Higher maternal pre-pregnancy body mass index (BMI) is associated with adverse pregnancy and perinatal outcomes. However, whether these associations are causal remains unclear.

Methods We explored the relation of maternal pre-/early-pregnancy BMI with 20 pregnancy and perinatal outcomes by integrating evidence from three different approaches (i.e. multivariable regression, Mendelian randomisation, and paternal negative control analyses), including data from over 400,000 women.

Results All three analytical approaches supported associations of higher maternal BMI with lower odds of maternal anaemia, delivering a small-for-gestational-age baby and initiating breastfeeding, but higher odds of hypertensive disorders of pregnancy, gestational hypertension, preeclampsia, gestational diabetes, pre-labour membrane rupture, induction of labour, caesarean section, large-for-gestational age, high birthweight, low Apgar score at 1 min, and neonatal intensive care unit admission. For example, higher maternal BMI was associated with higher risk of gestational hypertension in multivariable regression (OR = 1.67; 95% CI = 1.63, 1.70 per standard unit in BMI) and Mendelian randomisation (OR = 1.59; 95% CI = 1.38, 1.83), which was not seen for paternal BMI (OR = 1.01; 95% CI = 0.98, 1.04). Findings did not support a relation between maternal BMI and perinatal depression. For other outcomes, evidence was inconclusive due to inconsistencies across the applied approaches or substantial imprecision in effect estimates from Mendelian randomisation.

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Conclusions Our findings support a causal role for maternal pre-/early-pregnancy BMI on 14 out of 20 adverse pregnancy and perinatal outcomes. Pre-conception interventions to support women maintaining a healthy BMI may reduce the burden of obstetric and neonatal complications.

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Keywords Pregnancy, Body mass index, Triangulation, Mendelian randomisation

Background

Obesity is a leading preventable cause of ill health, mortality, and morbidity across the world and affects 10% and 25% of adult women in low- and high-income countries, respectively [1]. Higher maternal pre-pregnancy body mass index (BMI) is associated with a higher risk of various adverse pregnancy and perinatal outcomes, including pregnancy loss, gestational hypertension (GH), preeclampsia (PE), gestational diabetes mellitus (GDM), perinatal depression, caesarean deliveries, preterm birth (PTB), large for gestational age (LGA), and no breastfeeding initiation [2–12]. However, given the ethical and logistical challenges of conducting randomised controlled trials (RCTs) in pregnancy, most evidence in the field comes from conventional observational studies, which may be confounded by unmeasured or inaccurately measured maternal characteristics, such as socioeconomic position, age, parity, ethnicity, smoking, and alcohol intake.

Understanding the impact of maternal pre-pregnancy BMI on pregnancy and perinatal health is key to inform appropriate interventions aimed at preventing adverse outcomes and to predict their future burden in different populations. A better understanding of the potential causal role of BMI can be achieved by integrating multiple lines of evidence in a triangulation framework [13, 14], which can help overcome fundamental biases arising from the reliance on a single method (e.g. multivariable regression in observational studies). In this context, more credible causal inference can be made for findings in agreement across different analytical approaches with different strengths and limitations; while disagreement could decrease confidence in previous findings or highlight specifics of future research needs, for example where there is imprecision in results from some approaches.

The aim of this study was to explore the relation of maternal pre-/early pregnancy BMI (hereafter 'maternal BMI') with a wide range of pregnancy and perinatal outcomes by integrating evidence from multivariable regression, Mendelian randomisation, and paternal negative control. The combination of these three approaches provides a unique contribution to the evidence basis on the causal effect of maternal BMI given their different strengths and limitations. While findings from conventional observational studies using multivariable regression might be biased by residual confounding, Mendelian randomisation studies are less prone to such form of confounding but may be biased by weak instruments or unbalanced horizontal pleiotropy [15, 16]. The use of negative control designs, such as using paternal BMI as a negative control exposure, can reveal bias in associations of maternal BMI with adverse pregnancy and perinatal outcomes since paternal BMI is unlikely to affect these outcomes, but may be associated with unmeasured confounders in a similar way to maternal BMI (Fig. 1) [17, 18].

Methods

Study participants

Data were obtained from up to 446,526 women participating in 14 studies in Europe and North America as part of the MR-PREG collaboration [22] (Table 1). We included women who had available information on at least one outcome of interest, had a singleton birth, delivered a baby without a severe known congenital anomaly, and were of European ancestry since most studies included participants of European descent only or predominantly. Informed consent was obtained from all participants and study protocols were approved by the local, regional, or institutional ethics committees. Details of recruitment, data collection, and ethical approval of each study can be found in Additional file 1: Supplementary Methods [23–55].

Exposure measures

Maternal BMI in kg/m^2 was calculated from measured or self-reported weight and height data (Table 1). Weight data was collected before pregnancy in eight studies, before 20 weeks of gestation in three studies, and between 24 and 32 weeks of gestation in one study. Two studies did not have a measure of pre- or early-pregnancy BMI and could only contribute to the Mendelian randomisation analyses.
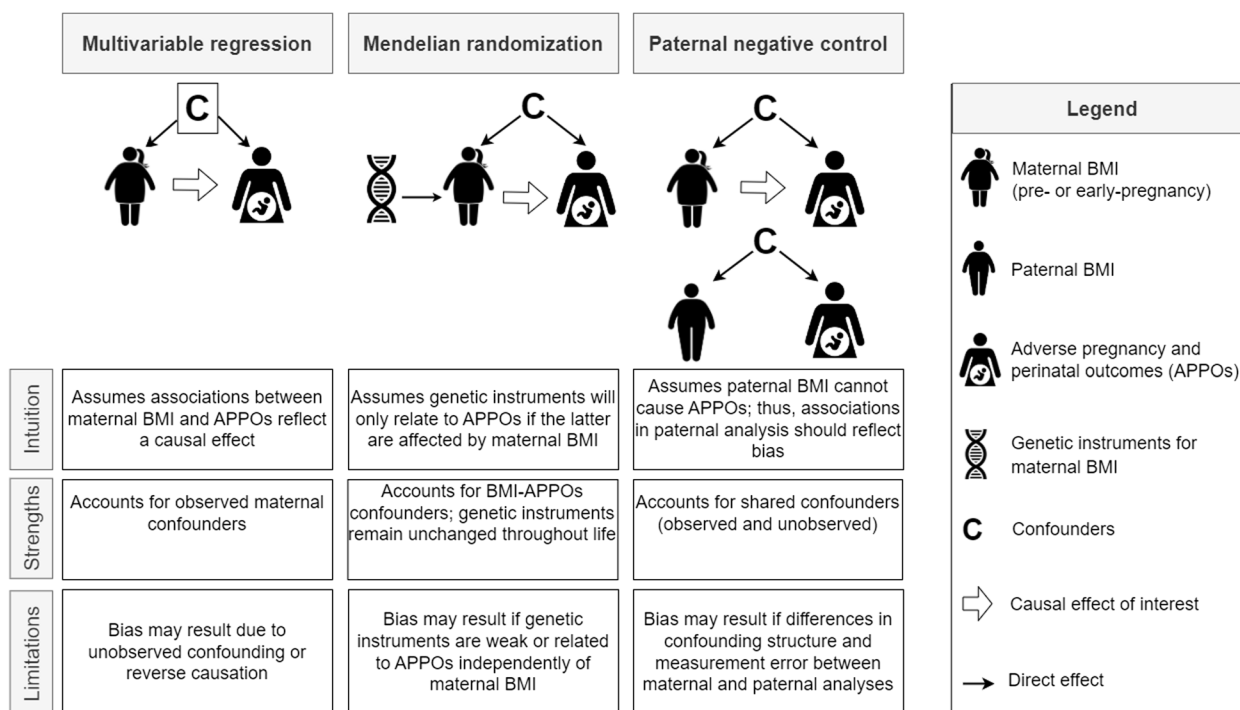
Fig. 1 Overview of the three analytical approaches used to investigate the effect of maternal body mass index on adverse pregnancy and perinatal outcomes. A brief description of each approach is presented in the context of exploring the effect of maternal BMI on APPOs' risk. Given each approach has different strengths and limitations, findings that agree across approaches are likely to be more credible. The description of each approach is simplified for illustration purposes. An extensive description of assumptions and sources of bias for each approach has been reported previously (e.g. [17–21]). The box around the confounders in the multivariable regression reflects the assumption of the method that all confounders were accurately adjusted for in the analyses. BMI, body mass index; APPOs, adverse pregnancy and perinatal outcomes

Outcomes measures

We focused on 20 a priori selected (based on clinical relevance and consensus amongst the study team) binary outcomes: miscarriage, stillbirth, hypertensive disorders of pregnancies (HDP), GH, PE, GDM, maternal anaemia, perinatal depression, pre-labour membrane rupture, induction of labour, caesarean section, PTB, LGA, small-for-gestational age (SGA), low birthweight, high birthweight, low Apgar score after 1 min, low Apgar score after 5 min, neonatal intensive care unit (NICU) admission, and breastfeeding initiation (see Table 2 for definitions and total sample sizes). We included related traits amongst the selected outcomes to maximise the number of cohorts contributing to the analyses (e.g. studies that did not have data on gestational age could contribute with information on low birthweight but not SGA). In additional analyses, we examined four continuous traits that underlie some of these outcomes (i.e. birthweight, birth length, ponderal index at birth, and gestational age at birth). Details on outcomes definitions, distributions, and sample sizes for each contributing study are available in Additional file 1: Supplementary Methods [23–55] and Additional file 2: Supplementary Tables 1A and B.

Covariables

The following were a priori considered potential confounders of the association between maternal BMI and the pregnancy and perinatal outcomes: maternal age, parity, education, smoking during pregnancy, and alcohol use during pregnancy. We also adjusted for offspring sex to improve statistical efficiency given its strong association with some outcomes (e.g. birthweight-related outcomes). Details of the distribution of these covariables in each study are provided in Additional file 2: Supplementary Table 2.

Statistical analyses

All analyses were conducted using Stata version 17 (StataCorp, College Station, TX) [59] or R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) [60]. Results are presented as odds ratio (OR) for each binary outcome per standard deviation (SD) increase in maternal BMI to facilitate the comparison of

Table 1 Characteristics of the included studies

Cohort	Source	Country	Year	Maximum N^a	BMI measurement	Maternal pre-pregnancy BMI [kg/m²]ᵇ Mean (SD)	Maternal age at delivery [years] Mean (SD)
ALSPAC*	[23, 24]	UK	1991–1992	11,272	Self-reported pre-pregnancy	22.95 (3.82)	28.46 (4.78)
BiB*	[26]	UK	2007–2010	5018	Measure around 12 weeks of gestation	26.63 (5.99)	26.82 (5.96)
DNBC-GOYA*	[28, 29]	Denmark	1996–2002	2542	Self-reported pre-pregnancy	23.59 (4.30)	29.67 (4.20)
DNBC-PTB (controls)*	[32]	Denmark	1996–2002	1676	Self-reported pre-pregnancy	23.44 (3.98)	29.78 (4.10)
EFSOCH*	[34]	UK	2000–2004	789	Weight self-reported pre-pregnancy, height measured during pregnancy	24.02 (4.43)	30.64 (5.03)
FinnGen	[37]	Finland	1969–2018	190,879	NA	NA	NA
GEN-3G	[56]	Canada	2010–2013	582	Self-reported pre-pregnancy	25.04 (5.70)	28.27 (4.34)
GenR	[41]	Netherlands	2002–2006	4138	Measured before 20 weeks of gestation	25.31 (4.89)	28.50 (5.66)
HAPO*	[43]	USA	1999–2002	1310	Measured between 24 and 32 weeks of gestation	28.46 (4.82)	31.31 (5.27)
INMA	[46]	Spain	1997–2011	1035	Self-reported pre-pregnancy weight, height measured in the first trimester	23.37 (4.25)	30.72 (4.02)
MoBa*	[47, 57]	Norway	1999–2008	81,795	Self-reported at 15 weeks gestation	24.05 (4.32)	30.13 (4.72)
NFBC1966	[49]	Finland	1966	356	Self-reported pre-pregnancy	25.14 (4.78)	30.22 (5.9)
NFBC1986	[51]	Finland	1986	883	Self-reported pre-pregnancy	24.17 (4.61)	25.43 (2.64)ᶜ
UK Biobank	[58]	UK	2006–2010	153,543	NA	NA	29.03 (6.34)ᵈ

Abbreviations: ALSPAC Avon Longitudinal Study of Parents and Children, *BiB* Born in Bradford, *DNBC-GOYA* Danish National Birth Cohort-Genetics of Obesity in Young Adults Study, *DNBC-PTB* Danish National Birth Cohort-Preterm Birth Study, *EFSOCH* Exeter Family Study of Childhood Health, *FinnGen* FinnGen (release 8), *GEN-3G* Genetics of Glycaemic Regulation in Gestation and Growth, *GenR* Generation R, *HAPO* Hyperglycaemia and Adverse Pregnancy Outcome, *INMA* Infancia y Medio Ambiente (English translation = Childhood and the Environment), *MoBa* Norwegian Mother, Father and Child Cohort Study, *NA* Not available, *NFBC1966* Northern Finland 1966 Birth Cohort, *NFBC1986* Northern Finland 1986 Birth Cohort

* Studies contributing to Mendelian randomisation analyses adjusted by offspring genotype

ᵃ Maximum number of mothers with data on at least one outcome

ᵇ Maternal BMI is only reported where collected pre- or early in pregnancy

ᶜ The relatively young age at delivery in the NFBC1986 cohort may be explained by the young age of the cohort at the time of the study

ᵈ Maternal age in UK Biobank was taken from maternity record linkage on a subsample of participants and may therefore not be representative of the full sample included

results. The analytical code is available at: https://github.com/gc13313/matbmi_preg.

Multivariable regression analyses

In the main analyses, we used logistic regression with two sets of adjustments: (1) maternal age and offspring sex and (2) additionally maternal education, parity, smoking during pregnancy, and alcohol use during pregnancy where available. We present the fully adjusted model as the main analyses and include the minimally adjusted model in the supplementary material. Similar multivariable linear regression models were used for the additional analyses with continuously measured outcomes. Study-specific results were combined using fixed-effects metanalyses (inverse-variance weighted) for the main analyses assuming that there is one true effect size underlying all included studies, and

random-effects metanalyses (*DerSimonian and Laird method*) for sensitivity analyses.

Mendelian randomisation analysis

We used two-sample Mendelian randomisation, in which the effect of interest is estimated by combining summary data for the association of single nucleotide polymorphisms (SNPs) with BMI and with each outcome, as summarised in Fig. 2 [61]. This approach allowed us to maximise statistical power by including all 14 studies in the analyses even when data on maternal BMI was not available (i.e. FinnGen and UK Biobank).

We selected 97 SNPs previously reported to be strongly associated with BMI ($P < 5x10^{-8}$) from a genome-wide association studies (GWAS) metanalysis conducted by the Genetic Investigation of ANthropometric Traits (GIANT) consortium (Additional file 2: Supplementary

Table 2 Case definition and sample size for pregnancy and perinatal outcomes across participating studies

Outcomes	Case definition	N	N cases	% cases
Binary outcomes				
Miscarriage[a]	Self-reported in index pregnancy	91,757	107	0.12%
	Self-reported in previous pregnancies	376,434	70,181	15.71%
Stillbirth[a]	Self-reported in index pregnancy	91,942	292	0.32%
	Self-reported in previous pregnancies	174,440	4613	2.58%
Hypertensive disorders of pregnancy	Gestational hypertension or preeclampsia[b]	416,803	26,867	6.06%
Gestational hypertension	Elevated blood pressure without proteinuria[b]	406,103	17,607	4.16%
Preeclampsia	Elevated blood pressure with proteinuria[b]	401,184	9827	2.39%
Gestational diabetes	Hyperglycaemia first diagnosed in pregnancy[c]	446,526	14,338	3.11%
Maternal anaemia	Maternal anaemia during pregnancy defined as Hb < 110 g/L (1st trimester) or Hb < 105 g/L(2nd or 3rd trimesters)	92,002	2425	2.57%
Perinatal depression	Self-reported diagnosis or assessed depression symptom scales	113,614	9320	7.58%
Pre-labour rupture of membranes*	Membrane rupture before the onset of contractions	249,265	19,339	7.20%
Induction of labour*	Labour needed induction	114,075	17,351	13.20%
Caesarean section*	Delivery by caesarean section	204,093	27,967	12.05%
Preterm birth*	Gestational age at birth < 37 weeks	261,473	14,090	5.11%
Large-for-gestational age*	> 90th percentile for z-score of birthweight accounting for sex and gestational age[d]	118,667	12,386	9.45%
Small-for-gestational age*	< 10th percentile for z-score of birthweight accounting for sex and gestational age[d]	118,667	8958	7.02%
Low birthweight*	Birthweight < 2500 g	247,716	14,964	5.70%
High birthweight*	Birthweight ≥ 4000 g	239,460	8142	3.29%
Low Apgar score at 1 min*	Apgar score at 1 min < 7	98,868	5760	5.51%
Low Apgar score at 5 min*	Apgar score at 5 min < 7	99,434	1167	1.16%
Neonatal intensive care unit (NICU) admission*	Neonate admitted to NICU	93,522	8262	8.12%
Breastfeeding initiation*	Ever breastfed	94,116	78,472	45.47%
Continuous outcomes				
Birthweight*	NA	326,537	NA	NA
Birth length*	NA	95,649	NA	NA
Ponderal index at birth*	NA	95,562	NA	NA
Gestational age at birth*	NA	118,723	NA	NA

Detailed information on each of the outcomes in each cohort is provided in Additional file 1: Supplementary material and Additional file 2: Supplementary table 1

[a] Miscarriage and stillbirths in the index pregnancy were used in multivariable regression and paternal negative control analyses, while miscarriage and stillbirth reported in previous pregnancies were used in Mendelian randomisation analysis

[b] Where possible, we applied the International Society for the Study of Hypertension in Pregnancy criteria (ISSHP), which defines any HDP as SBP ≥ 140 mmHg or DBP ≥ 90 mmHg, measured on two occasions after 20 weeks' gestation, with those who are then defined as having pre-eclampsia also having proteinuria (with the raised blood pressure) of at least 30 g/Dl and those defined as having gestational hypertension being those who do not meet criteria for pre-eclampsia. By contrast, in some studies (e.g. UK Biobank), information on diagnosis was extracted directly from medical records

[c] Criteria used to define hyperglycaemia first diagnosed in pregnancy varies across studies. Most studies obtained information from questionnaires (i.e. self-reported diagnosis) or from medical records [ICD-10 code O24]

[d] Different reference populations were used to calculate percentiles across studies

* For these a priori selected outcomes, additional Mendelian randomisation analyses were conducted accounting for offspring genotype

Table 3) [62]. Unlike more recent BMI GWAS [64], the cohorts included in this GWAS were largely independent from the studies included in our analyses avoiding potential biases due to sample overlap [65, 66].

Summary data for the SNP-BMI associations were obtained from the GIANT GWAS metanalyses of European females (Additional file 2: Supplementary table 3) [62], which included up to 171,977 women (~ 0.5% of participants were also included in our study). We estimated the strength of the genetic instruments using the mean F-statistic and total R^2 for the SNP-BMI association in the GIANT GWAS results as previously described [67, 68]. We also examined the correlation between SNP-BMI

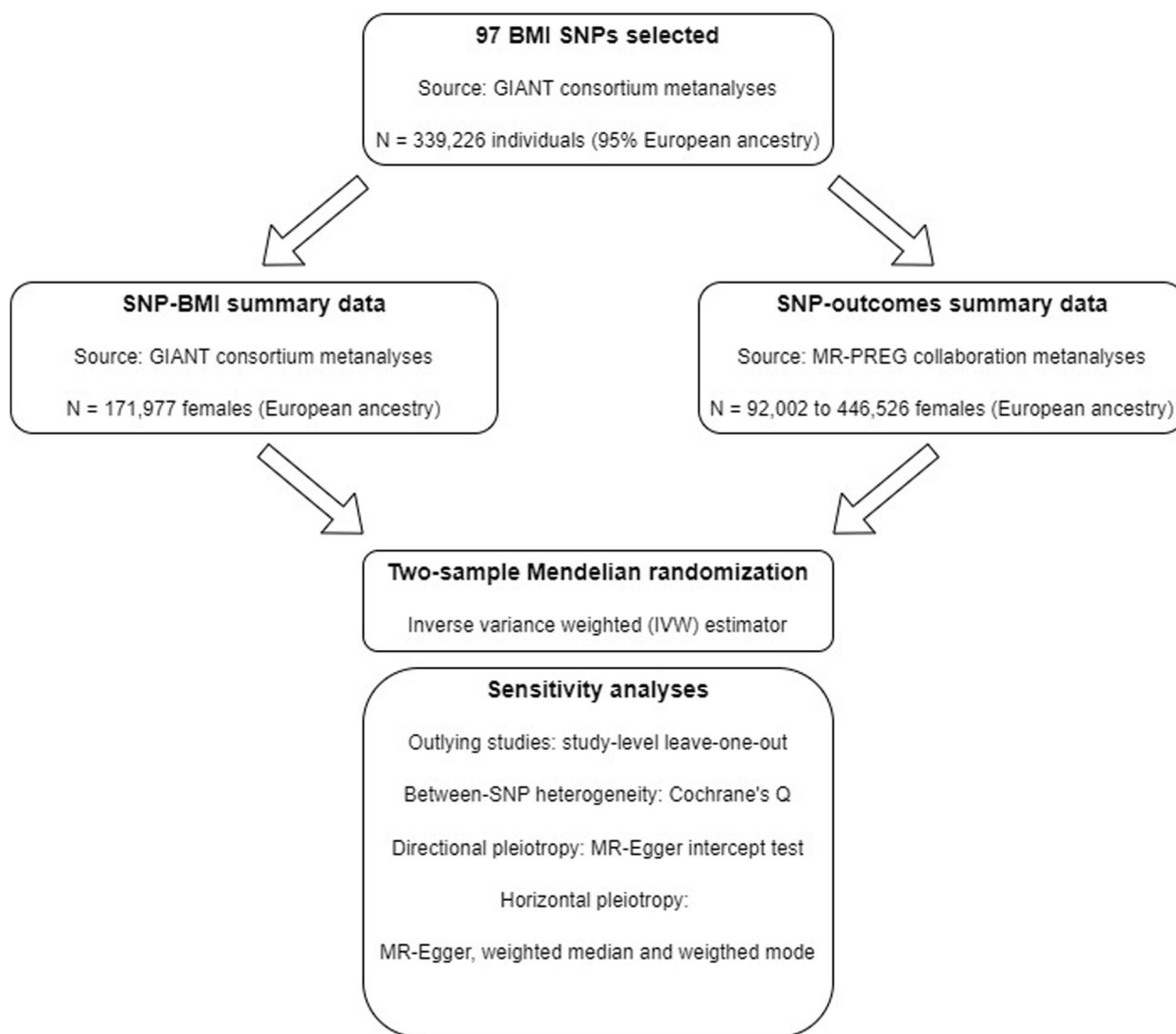Borges *et al. BMC Medicine*   (2024) 22:32

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Fig. 2 Overview of the two-sample Mendelian randomisation analyses framework. We selected 97 SNPs as instruments for maternal BMI from a genome-wide association studies (GWAS) metanalysis conducted by the Genetic Investigation of ANthropometric Traits (GIANT) consortium [62, 63], including 339,226 males and females. For the selected SNPs, we extracted summary data for the SNP-BMI associations from the GIANT GWAS metanalyses of European ancestry females (*N* = 171,977) and SNP-outcomes associations from European ancestry females from the MR-PREG collaboration (*N* range = 92,002 to 446,526). After harmonising SNP-BMI and SNP-outcomes' summary data, two-sample MR analyses were carried out using the inverse variance weighted (IVW) method, and a series of sensitivity analyses was performed to assess the plausibility of the core Mendelian randomisation assumptions as specified in the figure. For two studies (Generation R and INMA), summary data was only available to us for 32 SNPs reported in an earlier GIANT BMI GWAS [63], of which 12 SNPs overlapped with the 97 selected SNPs and were included in our metanalyses

estimates in non-pregnant (data from the GIANT consortium) and pregnant women (data from participating cohorts where information on maternal BMI was available to us).

Summary data for the SNP-outcomes associations were obtained from each contributing study using logistic (or linear) regression assuming an additive model. For each SNP, we meta-analysed cohort-specific SNP-outcome associations using inverse-variance weighted fixed-effects for the main analyses and random effects (*DerSimonian and Laird method*) for sensitivity analyses.

The main two-sample MR analyses were carried out using the inverse variance weighted (IVW) method [67]. In addition, we also conducted a leave-one-out analysis at the study level where the pooled IVW estimates were re-computed removing one study at a time to check whether pooled results were driven by a single study.

We conducted a series of sensitivity analyses to explore the plausibility of the core Mendelian randomisation assumption that any effect of SNPs on the outcomes is fully mediated by maternal BMI. We explored the potential presence of invalid instruments (e.g. due to SNPs affecting the outcomes through pathways not mediated by BMI) by (i) assessing between-SNP heterogeneity and directional pleiotropy in effect estimates using Cochran's Q-statistic and the MR-Egger intercept test [68], respectively, and (ii) using other Mendelian randomisation methods that are more robust to invalid instruments than IVW (MR-Egger [68], weighted median [69], and weighted mode [70]). For offspring outcomes (Table 2), we explored whether IVW estimates might be biased by genetic confounding since maternal BMI genetic variants might influence offspring outcomes (e.g. birthweight) due to the foetus inheriting these variants from the mother rather than due to a causal effect of maternal BMI on the intra-uterine environment [71–73]. This was done by repeating the IVW analyses using summary data for the SNP-outcomes associations adjusted for offspring genotype, which were obtained by regressing each outcome on the maternal genotype for each SNP including the offspring genotype for the respective SNP as a covariable in the model (all genotypes were coded as the number of BMI-increasing alleles).

Paternal negative control analyses

We used paternal BMI as a negative control exposure to explore whether the associations of maternal BMI with pregnancy and perinatal outcomes could be explained by residual confounding due to shared familial environment influencing BMI in both partners [18, 74]. These analyses included paternal BMI data from ALSPAC ($N = 2821–6952$), calculated from weight and height self-reported by the father during the first trimester; GenR ($N = 596–911$), measured during the first trimester; and MoBa ($N = 39,243–57,170$), reported by the mother at 15 weeks of gestation. We used multivariable regression to estimate the association of paternal BMI with the outcomes of interest adjusting (where available) for paternal age, number of children, education, smoking, and alcohol intake around the time of their partners' pregnancy, as well as their partners' BMI to account for the correlation between maternal and paternal BMI due to assortative mating or shared lifestyle [74, 75] (correlation coefficients ranging from 0.17 in ALSPAC to 0.24 in MoBa). Results were then contrasted between the mutually adjusted maternal and paternal BMI (negative control) analyses. The adjusted maternal regression estimates used for comparison with paternal BMI associations in the negative control analysis differ from the multivariable regression estimates used in the main analysis (that are

compared to the Mendelian randomisation estimates). In the paternal negative control comparison, the maternal regression estimates were additionally adjusted for paternal BMI and paternal confounders and therefore restricted to studies reporting both maternal and paternal BMI. Similar estimates between maternal and paternal BMI analyses indicate maternal BMI is unlikely to be a cause of pregnancy and perinatal outcomes via intrauterine mechanisms assuming comparable sources of biases. Conversely, associations that are specific or stronger in the maternal compared to the paternal BMI analyses would support a causal effect of maternal BMI.

Patient and public involvement

The current research was not informed by patient and public involvement because it used secondary data. This means that patients and the public were not involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. No study participants were asked to advise on interpretation or writing up of results. The results of the research will be disseminated to study participants on request, and to stakeholders and the broader public as relevant.

Results

Study and participant characteristics

The characteristics of the 14 included studies are shown in Table 1. Mean maternal BMI ranged from 23.0 to 28.5 kg/m^2 across studies, and mean maternal age ranged from 25 to 31 years old. The maximum sample size from each study ranged from 356 (NFBC1966) to 190,879 (FinnGen). The number of cases ranged from 107 for miscarriage in the index pregnancy (used in multivariable regression and paternal negative control analyses) to 78,472 for breastfeeding initiation (Table 2).

Main analyses results

Results for the main multivariable regression (fully adjusted model) and Mendelian randomisation (IVW) analyses are shown in Figs. 3 and 4 (binary outcomes) and Additional file 3: Supplementary Fig. 1 (continuous outcomes).

In the main multivariable regression analyses, maternal BMI was associated with 19 out of the 20 binary outcomes. Higher maternal BMI was associated with a higher risk of miscarriage, stillbirth, HDP, GH, PE, GDM, pre-labour membrane rupture, induction of labour, caesarean section, PTB, LGA, high birthweight, low Apgar score at 1 min, low Apgar score at 5 min, and NICU admission. In addition, women with higher BMI were less likely to have maternal anaemia, have a baby
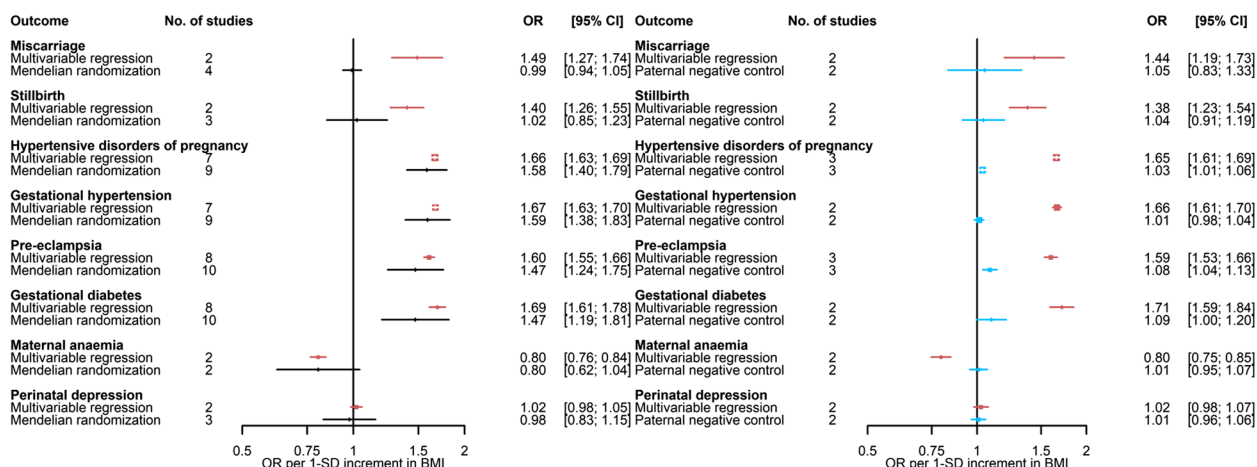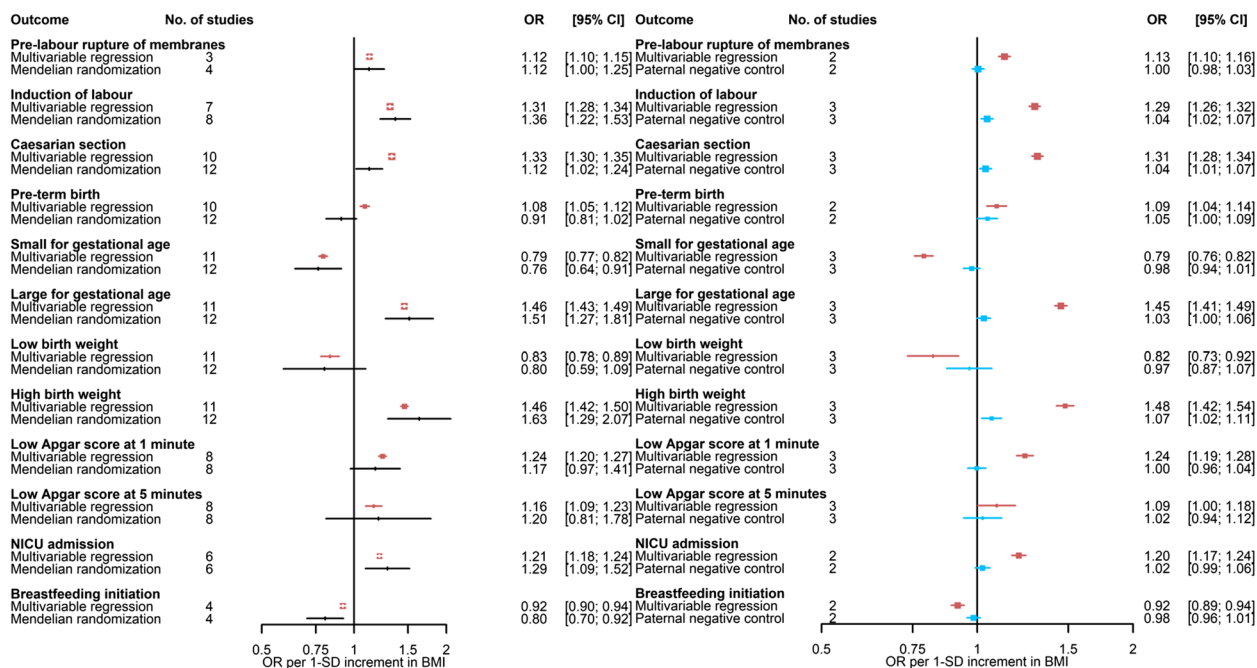
Fig. 3 Comparison of **A** adjusted multivariable regression and main Mendelian randomisation estimates and **B** mutually adjusted multivariable regression estimates and paternal negative control (exposure, paternal body mass index)—for the association of maternal body mass index with binary outcomes (Part 1). Paternal BMI was used as a negative control exposure to explore the potential presence, direction, and magnitude of bias in multivariable estimates for associations of maternal BMI with outcomes.. Results are expressed as odds ratios per SD unit of maternal BMI and paternal BMI for 'Multivariable regression' and 'Paternal negative control', respectively. Multivariable regression results were adjusted for paternal BMI, maternal age, parity, education, smoking during pregnancy, alcohol use during pregnancy, and offspring sex where available. Paternal negative control results were adjusted for maternal BMI, paternal age, number of children (ALSPAC only), paternal education, paternal smoking, paternal alcohol use, and offspring sex. BMI, body mass index; NICU, neonatal intensive care unit

Fig. 4 Comparison of **A** adjusted multivariable regression and main Mendelian randomisation estimates and **B** mutually adjusted multivariable regression estimates and paternal negative control (exposure, paternal body mass index)—for the association of maternal body mass index with binary outcomes (Part 2). Paternal BMI was used as a negative control exposure to explore the potential presence, direction, and magnitude of bias in multivariable estimates for associations of maternal BMI with outcomes.. Results are expressed as odds ratios per SD unit of maternal BMI and paternal BMI for 'Multivariable regression' and 'Paternal negative control', respectively. Multivariable regression results were adjusted for paternal BMI, maternal age, parity, education, smoking during pregnancy, alcohol use during pregnancy, and offspring sex where available. Paternal negative control results were adjusted for maternal BMI, paternal age, number of children (ALSPAC only), paternal education, paternal smoking, paternal alcohol use, and offspring sex. BMI, body mass index; NICU, neonatal intensive care unit

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SGA or with low birthweight, and initiate breastfeeding (Figs. 3 and 4). There was little evidence of maternal BMI being associated with the risk of perinatal depression (Fig. 3). Higher maternal BMI was associated with higher values of most continuous outcomes (i.e. birthweight, birth length, and ponderal index) (Additional file 3: Supplementary Fig. 1).

For the Mendelian randomisation analyses, we estimated that the total R^2 and mean F-statistic for the association of SNPs with BMI were 2.7% and 36, respectively, for the set of 97 SNPs using female-specific data from the GIANT GWAS. We observed a positive correlation ($r = 0.67$) between SNP-BMI estimates from females in the GIANT GWAS and SNP-BMI (pre-/early-pregnancy) estimates pooled across participating cohorts (Additional file 3: Supplementary Fig. 2). In agreement with multivariable regression analyses, findings from Mendelian randomisation indicated that higher maternal BMI is related to higher risk of HDP, GH, PE, GDM, pre-labour membrane rupture, induction of labour, caesarean section, LGA, high birthweight, low Apgar score at 1 min, NICU admission, lower risk of having maternal anaemia, a SGA baby, lower odds of initiating breastfeeding, and not associated with perinatal depression. On the other hand, in contrast with multivariable regression analyses, Mendelian randomisation findings did not provide support for a positive association of maternal BMI with miscarriage, stillbirth, and PTB. As expected, given the lower statistical power, confidence intervals were wider for Mendelian randomisation compared to multivariable regression analyses and included the null value for some of these outcomes (Figs. 3 and 4). For two binary outcomes (i.e. low Apgar score at 5 min and low birthweight), it was less clear whether estimates from multivariable and Mendelian randomisation are in agreement given the substantial uncertainty in the latter. For most continuous outcomes (i.e. birthweight, birth length, and ponderal index), findings from Mendelian randomisation indicated that higher maternal BMI was associated with higher values of continuous outcomes in agreement with multivariable regression analyses (Additional file 3: Supplementary Fig. 1).

Paternal negative control results supported the role of maternal BMI on stillbirth, HDP, GH, PE, GDM, maternal anaemia, pre-labour membrane rupture, induction of labour, caesarean section, SGA, LGA, high birthweight, low Apgar score at 1 min, NICU admission, and breastfeeding initiation (Figs. 3 and 4). The association of paternal BMI with maternal perinatal depression was also close to the null, consistent with maternal multivariable and Mendelian randomisation results. Associations with miscarriage, PTB, low birthweight, and low Apgar score at 5 min were imprecise and/or more similar in direction and magnitude between paternal and maternal BMI analyses. Results for continuous outcomes were strongly attenuated for paternal BMI in relation to birthweight and length (Additional file 3: Supplementary Fig. 3).

Sensitivity analyses

Overall, findings from the main multivariable regression analyses were consistent across studies (Additional file 3: Supplementary Fig. 4), when using random-effect metanalyses (Additional file 3: Supplementary Fig. 5), and with minimally adjusted models (Additional file 3: Supplementary Fig. 6). Between-study heterogeneity was substantial (i.e. Cochrane's Q p-value < 0.05) for GDM, maternal anaemia, low Apgar score at 1 min, gestational age, and birthweight (Additional file 3: Supplementary table 4).

Overall, findings from the main Mendelian randomisation analyses were not driven by any individual study as indicated by the leave-one-out analyses, although in some cases removing one study resulted in attenuation and substantial imprecision of effect estimates, such as for GDM when removing FinnGen and for delivery outcomes when removing MoBa (Additional file 3: Supplementary Fig. 7). Results were similar when using fixed- or random-effect meta-analyses to pool SNP-outcome estimates across studies (Additional file 3: Supplementary Fig. 8). There was evidence of substantial SNP heterogeneity in the IVW analyses of maternal BMI with 11 out of 20 binary outcomes and 1 out of 4 continuous outcomes (Additional file 2: Supplementary table 5). Despite that, there was no clear evidence of directional pleiotropy as evidenced by the MR-Egger intercept test (except for GDM and gestational age) (Additional file 2: Supplementary table 5). Furthermore, Mendelian randomisation results were generally consistent when using different Mendelian randomisation methods (Additional file 3: Supplementary Fig. 9), although estimates from MR-Egger were imprecise for some outcomes. Effect estimates adjusting for offspring genotype were more imprecise due to the smaller sample size; however, overall, point estimates were not substantially different compared to the main analyses with a few exceptions, such as pre-labour rupture of membranes, LGA, and high birthweight, where adjusted results were attenuated (Additional file 3: Supplementary Fig. 10).

Findings from the main paternal negative control analyses were consistent between studies (Additional file 3: Supplementary Fig. 11 for maternal associations additionally adjusted for partners BMI and Additional file 3: Supplementary Fig. 12 for paternal associations) and when comparing different models (Additional

file 3: Supplementary Figs. 13–15). Findings from the main multivariable regression analyses were similar when stratified by BMI taken pre-pregnancy compared to during pregnancy (Additional file 3: Supplementary Fig. 16).

Discussion

By triangulating different analytical approaches, our findings are compatible with higher maternal BMI being causally related to 14 out of 20 pregnancy and perinatal outcomes, including a higher risk of HDP, GH, PE, GDM, pre-labour membrane rupture, induction of labour, caesarean section, LGA, high birthweight, low Apgar score at 1 min, NICU admission, and lower odds of maternal anaemia, SGA, or breastfeeding initiation. In addition, we did not find supportive evidence for a relation of maternal BMI with perinatal depression. For other outcomes, evidence is uncertain due to inconsistencies across multiple approaches (i.e. multivariable regression results for miscarriage, stillbirth, and PTB were not supported by Mendelian randomisation) or substantial imprecision in effect estimates from Mendelian randomisation (i.e. low birthweight and low Apgar score at 5 min).

Consistent with our results, a previous study using multivariable regression reported higher maternal BMI (across the whole distribution) was associated with increased risk of HDP, GDM and LGA, and reduced risk of SGA based on data from 265,270 mother–offspring pairs (samples partly overlapping with our study) [10]. In addition, there was some evidence of a non-linear association with odds of PTB, which were higher in women who were underweight or obese [10]. In agreement with these findings, a larger study (9,282,486 mother–infant pairs in the USA) focussed on offspring outcomes indicated that higher maternal BMI was associated with a higher risk of high birthweight, LGA, and low Apgar score and reported a non-linear relationship with PTB risk [76]. Other observational studies using multivariable regression have reported that maternal BMI is associated with a higher risk of stillbirths [77], induction [78], caesarean section [78], and not initiating breastfeeding [79]. Previous Mendelian randomisation studies have focused on a limited set of outcomes and are supportive of higher maternal BMI being related to higher mean offspring birthweight [4, 27, 80] ($N \sim 9{,}000$ to 400,000) and GDM [81] ($N = 5485$ cases and 347,856 controls).

Recent systematic reviews of randomised controlled trials (RCTs) of diet and physical activity during pregnancy (*N* range: 12,526–34,546) reported some evidence of reduced risk of GDM, LGA, and caesarean section in those randomised to the intervention, but no effect or mixed results of the intervention on HDP, PTB, and NICU admission [82–84]. Of note, these studies aimed at managing weight gain during pregnancy rather than targeting weight reduction prior to pregnancy with a modest mean difference of -0.7 to -1.2 kg between women in the intervention compared to those randomised to standard care. In addition, evidence for many outcomes is uncertain due to the relatively small number of cases.

Although mechanisms are not fully understood, higher maternal BMI is likely to influence a range of processes that are involved in the aetiology of some of the outcomes of interest, such as insulin resistance, endothelial dysfunction, inflammation, and susceptibility to infection [85]. In addition, maternal dysmetabolism resulting from excess adiposity has a well-recognised impact on maternal circulating nutrients, such as glucose, lipids, and amino acids, some of which can cross the placenta and influence offspring outcomes, such as growth [4, 86, 87].

Strengths and limitations

Key strengths of this study include exploring the potential role of maternal BMI on a wide range of pregnancy and perinatal outcomes in large samples from multiple studies using different approaches. The credibility of findings from each approach relies on the plausibility of assumptions that are often not possible to verify, such as no unmeasured confounding in multivariable regression, similar confounding, selection and measurement error between paternal and maternal BMI analyses, and no confounding or horizontal pleiotropy in Mendelian randomisation. Therefore, results in agreement across approaches strengthen the evidence on the relation of maternal BMI with the outcome. Where possible, we explored the plausibility of assumptions underlying each method. In particular, we conducted extensive sensitivity analyses to explore the plausibility of the core Mendelian randomisation assumptions and found overall these did not suggest Mendelian randomisation results were driven by weak, invalid instruments or confounding by offspring genotype.

Key limitations of this study are as follows. First, despite the large scale of our study, statistical power varied across outcomes as some outcomes have lower prevalence and/or were not collected in all cohorts. Second, despite our efforts to capture the best and most homogeneous definition for outcomes across studies, this was not always possible as exemplified by GDM, for which the data collected was notably variable across studies (e.g. from self-report to medical records-derived information), and index miscarriage (which was used for multivariable regression and paternal negative control analyses but is poorly captured in birth cohorts during the early pregnancy period). Third, while we were interested in maternal pre-pregnancy BMI, only maternal weight

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reflecting early-/mid-pregnancy was available in four studies. Fourth, our analyses assumed a linear effects of BMI, which may not be the case for some outcomes like PTB, and were restricted to women of European ancestry given most studies had scarce data on women from other ancestries. While this reduces the risk of confounding by ethnicity or population structure, it may limit the generalisability to other populations of pregnant women.

Conclusions

Our findings support a causal role for higher maternal BMI on a range of adverse pregnancy and perinatal outcomes. Given the high prevalence of overweight and obesity, our findings emphasise the need for development and testing of pre-conception interventions to support women maintaining a healthy BMI. This should be a key target to reduce the burden of obstetric and neonatal complications.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-023-03167-0.

Additional file 1. Supplementary methods.

Additional file 2. Supplementary tables.

Additional file 3. Supplementary figures.

Authors' contributions

DAL designed the study. MCB and GLC developed the analysis plan, performed data analyses, and wrote the first draft of the manuscript. RMF, JFF, AFS, AGS, FK, QY, RRCM, RCR, XL, LS, AI, ATH, BB, DMS, EAN, TAB, MGH, JW1, JT, JW2, LB, MM1, MB, MCH, MRJ, MV, PP, PM, RG, VWVJ, WLLJ, BF, MFH, TIAS, SHE, SS, and MM2 have made substantial contributions to acquiring data, analysing study-specific data, interpreting results, and revising the draft for important intellectual content. MCB, GLC, and DAL will act as guarantors of the study. All authors read and approved the final version of the manuscript.

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Availability of data and materials

In order to protect participant confidentiality, supporting data cannot be made openly available. Bona fide researchers can apply for access to study-specific executive committees. Summary association data for FinnGen is publicly available at https://www.finngen.fi/en/access_results. Researchers can apply for access to the UK Biobank data via the Access Management System (AMS) (https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access).

Declarations

Ethics approval and consent to participate

ALSPAC: Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (NHS Haydock REC: 10/H1010/70).
BiB: Ethical approval for the study was granted by the Bradford National Health Service Research Ethics Committee (ref 06/Q1202/48).
DNBC-GOYA: The study was approved by the regional scientific ethics committee and by the Danish Data Protection Board.
DNBC-PTB: Ethical approval was obtained from the Regional Scientific Ethical Committee of Copenhagen and the study was also approved by the Danish Data Protection Agency.
EFSOCH: All women gave informed consent and ethical approval was obtained from the local review committee.
FinnGen: The Coordinating Ethics Committee of the Helsinki and Uusimaa Hospital District has approved the FinnGen consortium (Nr HUS/990/2017), and the ethical approval of each individual study has been described in detail elsewhere [35].
Gen3G: Ethics approval was obtained from the Centre Hospitalier Universitaire de Sherbrooke (CHUS) Ethics Review Board for Studies with Humans.

Generation R: The study protocol was approved by the Medical Ethical Committee of the Erasmus MC, University Medical Center Rotterdam and informed consent was obtained for all participants.

HAPO: The protocol was approved by the institutional review board at each field center. All participants gave written informed consent. An external data and safety monitoring committee provided oversight.

INMA: Informed consent was obtained from all participants and the study was approved by the Hospital Ethics Committees in each participating region.

MoBa: The establishment of MoBa and initial data collection was based on a licene from the Norwegian Data Protection Agency and approval from The Regional Committees for Medical and Health Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The current study was approved by The Regional Committees for Medical and Health Research Ethics of South/East Norway (ref 2018/1256).

NFBC1966 and 1986: An informed consent for the use of the data including DNA was obtained from all subjects. NFBC1966 received ethical approval from the Ethics Committee of Northern Ostrobothnia Hospital District (EETTMK: 94/2011) and Oulu University, Faculty of Medicine, Oulu, Finland. NFBC1986 received ethical approval from the Ethics Committee of Northern Ostrobothnia Hospital District (EETTMK: 108/ 2017) and Oulu University, Faculty of Medicine, Oulu, Finland.

UK Biobank: Ethical approval for UKB was obtained from the North West Multicentre Research Ethics Committee (MREC), and our study was performed under UKB application number 23938.

Details of ethical approval and consent to participate of each study can also be found in Additional file 1: Supplementary Methods.

Consent for publication
Not applicable.

Competing interests
DAL receives support from several national and international government and charitable research funders, as well as from Medtronic Ltd and Roche Diagnostics for research unrelated to that presented here. The other authors declare that they have no competing interests.

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