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Network

Abstract

International sharing of cohort data for research is important and challenging. We explored the feasibility of multi-cohort federated analyses by examining associations between three pregnancy exposures (maternal education, exposure to green vegetation and gestational diabetes) with offspring BMI from infancy to 17 years. We used data from 18 cohorts (n=206,180 mother-child pairs) from the EU Child Cohort Network and derived BMI at ages 0-1, 2-3, 4-7, 8-13 and 14-17 years. Associations were estimated using linear regression via one-stage IPD meta-analysis using DataSHIELD. Associations between lower maternal education and higher child BMI emerged from age 4 and increased with age (difference in BMI z-score comparing low with high education age 2-3 years = 0.03 [95% CI 0.00, 0.05], 4-7 years = 0.16 [95% CI 0.14, 0.17], 8-13 years = 0.24 [95% CI 0.22, 0.26]). Gestational diabetes was positively associated with BMI from 8 years (BMI z-score difference = 0.18 [CI 0.12, 0.25]) but not at younger ages; however associations attenuated towards the null when restricted to cohorts which measured GDM via universal screening. Exposure to green vegetation was weakly associated with higher BMI up to age one but not at older ages. Opportunities of cross-cohort federated analyses are discussed.

Introduction

Prospective cohort studies contribute to important research questions, but they are resource intensive. Over recent decades, international funders and cohort data custodians have emphasised the importance of data sharing [1-4]. This provides economic efficiency, enables replication and triangulation of findings across different studies, increases the period of the life course that can be studied for repeated measures, and increases statistical power particularly for rare outcomes.

To meet this challenge, the EU Child Cohort Network (EUCN) has been created to address key research questions about the associations of early life stressors with health from infancy to adulthood [5, 6]. The EUCN is an open and sustainable network of 17 birth cohorts across 12 countries in Europe and Australia comprising more than 250,000 participants. In addition to increasing power and supporting replication, this network contains extensive repeated-measured data and thus enables researchers to explore how associations might differ across the life course.

The aim of this paper is to use the EUCN to explore the feasibility of multi-cohort federated analyses ('federated' describes the analysis of multiple datasets) by examining associations between different pregnancy exposures and offspring BMI from infancy to 17 years. BMI was chosen as a suitable outcome for this proof-of-concept study as reducing childhood overweight and obesity is a major global public health challenge and it is hypothesised that higher BMI starts to be 'programmed' in intrauterine and early infancy [7, 8]. Furthermore, as weight and height are often measured at repeated time points it provides an opportunity to investigate potential changes in exposure-BMI associations at different ages across the life course.

We chose three pregnancy exposures which were hypothesised to influence offspring BMI and that would be useful to illustrate different challenges in federated analyses (e.g. harmonisation and missingness): (i) maternal education, (ii) exposure to green vegetation and (iii) gestational diabetes (GDM). We chose maternal education as an example of a categorical variable with low levels of missing data in EUCN for which there is extensive previous research on associations with BMI. We chose exposure to green vegetation as a continuous, area-based variable, with high levels of missing data because of some cohorts in EUCN not having geographic data. Finally, we chose GDM as a categorical variable harmonised from diverse sources of information (e.g. retrospective self-report, health record extraction and diagnosis made on the basis of results from blood samples). The exposures are briefly summarised below.

Maternal education. Socioeconomic position (SEP) is a complex exposure encompassing several different domains of family resources with maternal education at birth a commonly used indicator. Lower maternal education birth is associated with higher child BMI in medium and high-income countries [9-14]. SEP likely influences childhood BMI through exposure to an obesogenic environment [15-17]. Whilst studies have consistently found lower family SEP to be associated with higher child BMI, evidence regarding the age at which these inequalities emerge and the course they take is not consistent. [9-13, 18, 19].

Residential Proximity to green space. Maternal availability of green spaces could influence offspring BMI via increased physical activity during pregnancy, stress reduction or reduced exposure to pollution [20, 21]. Some studies have reported that higher postnatal exposure to green spaces is associated with lower BMI, but evidence is not conclusive [22-24]. Whilst

increased prenatal exposure to green spaces has been consistently associated with higher birth weight [25, 26], little is known about associations with BMI at older ages [27].

Gestational Diabetes Mellitus (GDM, **defined as hyperglycaemia in pregnancy)** [28] is robustly associated with higher mean birth weight and large for gestational age [29-32]. Higher birth weight is in turn associated with higher future offspring BMI, fat mass and lean mass [33, 34] thus it has been proposed that intrauterine fetal overgrowth related to higher maternal circulating glucose may result in lifelong higher offspring BMI [35, 36]. However, few studies have explored whether any association of GDM with offspring BMI changes as the offspring age. This is important as a lasting effect into older age and/or an increasing effect across both childhood and adulthood might lead to higher risk of adverse adult cardiometabolic outcomes than association limited only to childhood [37].

The aims of this study therefore were to explore the feasibility of multi-cohort federated analyses by examining associations between three pregnancy exposures (maternal education, green spaces and GDM) and BMI measured at 5 age periods across childhood. We hypothesised that those whose parents had lower educational attainment, and those exposed in-utero to maternal gestational diabetes would have higher BMI. As evidence for the association of maternal gestational access to green space and offspring BMI is limited we had no specific hypothesis for the association.

Methods

Inclusion criteria and participating cohorts

Pregnancy and birth cohort studies from the ECCN were eligible to participate if they (i) had information on at least one of the four exposures and BMI measured at a minimum of one

time point, (ii) the study was approved by their institutional review boards, and (iii) the

infrastructure for federated analysis was established. Further details of each cohort can be

found in Jaddoe et al. [5] and each cohort's profile paper. All 17 core cohorts were invited,

plus two additional cohorts from the wider LifeCycle network which had harmonised data

available (The Amsterdam Born Children and their Development cohort, ABCD [38] and The

Healthy Growth Study, HGS) [39]. Of these 19 studies, 18 were able to participate (the

Helsinki Birth Cohort Study was unable to participate as they had not implemented the

required infrastructure; Table 1). The analysis sample thus consisted of these 18 cohorts with

a maximum sample size of n = 206,180 (Figure 1). All participants gave written informed

consent and ethical approval was granted by local ethics boards (Web Appendix 2). The

analysis plan can be viewed at https://osf.io/58vau/.

Exposures

Maternal education at birth

A harmonised maternal education variable was created in each cohort based on the

International Standard Classification of Education 97 (ISCED-97) and consisted of three

categories: Low (No education to lower secondary; ISCED-97 categories 0-2), Medium

(Upper and post-secondary; ISCED-97 categories 3-4), High (Degree and above; ISCED-97

categories 5-6) [40]. Data was available in all cohorts.

Green spaces

Exposure to green space during pregnancy was captured using Normalized Difference

Vegetation Index (NDVI) within a 300m buffer from the residential address using

Geographic Information System approaches previously described [41]. NDVI (range 0-1)

quantifies vegetation by measuring the difference between near-infrared and red-light

reflection based on satellite imagery. Extremely low values (0 - 0.1) indicate areas of barren

rock, sand or snow; moderate values (0.2 - 0.5) indicate sparse vegetation such as shrubs and

grasslands, whilst high values (0.6 - 1) indicate dense vegetation [42]. Data was available for

nine cohorts (ALSPAC, BiB, DNBC; EDEN; GEN R; INMA; MoBa, NINFEA, Rhea).

Gestational diabetes

A binary variable indicating the presence or absence of evidence for GDM was harmonised

for each cohort based either on extraction from clinical records or maternal self-report (Web

Table 1). Data was available for all cohorts except HGS, NFBC66 and NFBC86. For most of

the included cohorts at the time of pregnancy no universal diagnostic test was used, meaning

that selective misclassification of some women with GDM being treated as 'healthy',

particularly if they had no clear risk factors for GDM, is possible. To test this, we performed

a sensitivity analysis only in those studies in which all women in the sample had a blood

measure of hyperglycaemia, including HbA1c, fasting or random glucose, oral glucose

challenge or tolerance test (BiB & Eden).

Outcome

The outcome was offspring BMI z-scores based on either clinic or parental reported height

and weight measurements (Web Table 2). Sex-and-age specific z-scores were calculated per

month for BMI using external WHO standards [43] and references [44] excluding

observations ±5 standard deviations from the population median. Separate BMI z-scores were

calculated for five age periods defined *a priori*: (i) 0 to 1 years, (ii) 2 to 3 years, (iii) 4 to 7

years, (iv) 8 to 13 years, (v) 14 to 17 years. These represent key developmental periods of

change (early infancy, pre-school, adiposity rebound, puberty and late adolescence). Only

one measurement per child was included within each period; therefore if children had more

than one measurement within an age bracket we used the earliest. A summary of the number

of observations provided by each child is provided in Web Table 3.

Confounders

We defined confounders as any factor that plausibly causes the exposure and offspring BMI,

and used Directed Acyclic Graphs (DAGs) to depict these and determine whether there was

any evidence of colliders that we should not adjust for (Web Figure 1). All confounders were

assessed via self-report except pre-pregnancy BMI which was based on either self-report or

clinical measurements of weight and height. For analyses of maternal education with

offspring BMI no confounders were included as we did not identify plausible causes of

variation in both maternal education and offspring BMI. For analyses with NDVI as exposure

we adjusted for maternal education, area deprivation and parity. For analyses with GDM as

the exposure we adjusted for maternal education, maternal age at birth (years), maternal pre-

pregnancy BMI (kg/m^2), parity (nulliparous, multiparous) and maternal smoking during

pregnancy (yes/no). In addition, all analyses were adjusted for cohort, child sex and age at

weight and height measurements (months) to improve statistical precision. All cohorts had

some available data on the above confounders. Maternal ethnicity also fit our definition of a

confounder for all exposures but was only available (defined as Western vs other) in 8 of the

17 cohorts (ABCD, ALSPAC, BiB, ELFE, GECKO, GEN-R, INMA & Raine; maximum N =

45,601 representing 22% of the 206,180 participants). In a sensitivity analyses we repeated

all analyses in this subset of cohorts with additional adjustment for ethnicity.

Federated analyses using DataSHELD

All analyses were performed using DataSHIELD version 6.1.0 and R version 3.5.2 [45].

Briefly, each participating cohort stored their harmonised data on a local server protected by

a firewall. Researchers granted permission to access the data use DataSHIELD to conduct

remote analysis of individual participant data. DataSHIELD provides data security by

preventing researchers viewing, copying or transferring any data. Instead, analysis commands

are performed on each server and only non-disclosive summary statistics returned to the

researcher.

The functionality available within DataSHIELD is continually being developed, however at

the time of writing mixed effects models were not available. Therefore, associations between

each exposure and BMI at each age period were tested using linear regression and one-stage

Individual Participant Data (IPD) meta-analysis. For each exposure we fit five separate

regression models where the outcome was child BMI z-score calculated within each age

period as described above. All regression models included a dummy variable for cohort and

were adjusted for confounders as described above. To explore potential selection bias (due to

each cohort contributing different data at different ages), we repeated all analyses restricting

the sample to the subgroup of participants with data at the oldest age. We also repeated

analyses using two-stage IPD random effects meta-analysis to describe estimates within each

cohort and explore between-cohort heterogeneity. We also assessed the influence of two large

cohorts (DNBC & MoBa) by repeating analyses with these cohorts excluded.

Missing data

The analysis sample consisted of participants with available data on at least one exposure and

BMI in at least one outcome period. There were minimal differences between participants in

the analysis sample and those excluded, except included participants were of slightly lower

education and had lower rates of smoking in pregnancy (Web Table 4). Multiple imputation

was also not available within DataSHIELD, therefore missing data were handled through

complete case analysis, with the percentage of participants who were complete cases ranging from 6% to 65% of eligible participants from all cohorts combined; the proportion with complete data decreased with increasing age (Web Table 5). In addition to attrition across all cohorts, one reason for the low percentage of complete cases in the oldest age bracket was that for one of the largest cohorts (DNBC) only a small percentage of children had reached this age at the time of analysis. Estimates from linear regression models using complete cases are unbiased if the chance of being missing is not associated with the outcome after adjusting for covariates [46]. To explore this assumption, for each exposure-outcome analysis we derived a variable indicating whether each participant had complete data. We then regressed this variable on child BMI adjusting for non-missing covariates (Web Figure 2). For all exposures, associations between BMI at all ages and the chance of having complete data were close to null.

Results

Participants' characteristics

The number of participants included in analyses ranged from 206,180 (maternal education and BMI ages 0-1) to 7,096 (NDVI & BMI at ages 14-17). There were large differences between cohorts in the education level of mothers, with MoBa and NINFEA containing mostly highly educated mothers whilst BiB, NFBC66 and Raine contained mothers with lowest levels of education (Figure 2a). INMA, NINFEA and Rhea had the lowest values for NDVI indicating exposure to lower levels of vegetation (Figure 2b). There was marked heterogeneity between cohorts in estimated rates of GDM (e.g. Gen-R = 0.8%, NINFEA = 8.1%; Figure 2c). Cohort-specific information on covariates and child BMI, height, weight and age at measurement are shown in Web Tables 6-10.

Associations between pregnancy exposures and child BMI

Figures 3-5 show associations between each exposure and BMI z-scores within each age period. At ages 0-1 and 2-3 years associations between maternal education and BMI were close to null; however, at older ages a consistent pattern emerged with lower maternal education associated with higher childhood BMI (Figure 3). There was some evidence of a linear relationship as the magnitude of the association increased across categories of maternal education. Associations at earlier ages were slightly weaker when restricting analyses to the subgroup of participants with data at the oldest age. Results were similar using 2-stage IPD (Web Figures 3a & 3b), and whilst there was considerable heterogeneity between cohorts (I^2 range 0-92%) the direction of association was largely consistent.

At ages 0-1 higher NDVI in pregnancy was associated with slightly higher BMI, however at older ages associations were close to null (Figure 4). Repeating analyses using 2-stage IPD showed considerable heterogeneity between cohorts (I^2 range 0-66%): for example at age 2-3 higher NDVI was associated with higher BMI in BiB but lower BMI in Rhea (Web Figure 4).

Between ages 0-7 associations between GDM and childhood BMI was close to null; however at ages 8-13 GDM was associated with higher BMI (Figure 5). Associations at all ages, except 0-1, were stronger when restricting to the subgroup of participants with data at the oldest age. These results were replicated using 2-stage IPD with 10 out of 13 cohorts showing a positive association at ages 8-13 ($I^2 = 0 - 78\%$; Web Figure 5). At ages 14-17 associations attenuated towards null, however within this age period only three cohorts had available data.

Sensitivity and subgroup analyses

To test for potential confounding by indication, we repeated analyses for GDM comparing cohorts where assessment was via a universal blood-based glucose test vs self-report or non-universal test, and found estimates to be lower for the two cohorts that used a universal blood-based test (Web Table 11). We additionally adjusted for ethnicity in the subset of up to 45,601 participants with available data, which attenuated associations of maternal education towards the null (Web Table 12). Finally we repeated analyses removing the two largest cohorts (DNBC and MoBa; Web Table 13), however this did not change the direction of any associations or markedly change their magnitude.

Discussion

In this IPD meta-analysis of 18 cohort studies with a maximum sample of 206,180 children we explored the feasibility and utility of multi-cohort federated analysis by examining associations between key pregnancy exposures and BMI across childhood. We found consistent evidence that lower maternal education was associated with increased childhood BMI. Replicating and extending previous research [10-13, 18], we found this association to emerge from ages 4-7 and increase in magnitude with age. Consistent with previous studies showing a positive association between exposure to green vegetation and birthweight [26, 27, 48, 49], we found that higher NDVI was associated with slightly higher BMI in the first year of life; although associations at older ages were close to null. We also found evidence that GDM was associated with higher child BMI at ages 8-13 but not at younger ages.

Opportunities and challenges of federated data analysis

Data harmonisation

In the EU Child Cohort Network[5], we were interested in average associations across studies that were largely from different European countries, with a small number of studies from

other high-income countries (e.g. Australia). As such a substantial effort was made to harmonise data across all contributing studies [5, 6]. Data harmonisation is also commonly undertaken in non-federated analyses, therefore the opportunities and challenges discussed herein will have relevance to other analysis attempting to estimate average associations across studies using consistent data.

Individual participant pooling of studies (whether federated or not) provides the opportunity to increase statistical power and obtain more precise estimates than any single cohort, and to explore robustness of associations by examining consistency (replication) across independent populations. However, harmonisation of data assessed in different ways and to different levels of detail can result in between study heterogeneity that could complicate interpretation of results. For example, if different studies have used different methods for a binary variable, there may be different levels of misclassification between studies that are disguised by the harmonised binary variable.

As noted in the methods and results above, this was a concern for the harmonised GDM variable. For most studies this was assessed via self-report, in populations where policy dictated diagnostic tests were only done in those with risk factors at the first antenatal clinic visit, which could introduce confounding by indication. To explore this, we undertook a sensitivity analysis comparing pooled results from the two studies that had diagnosed GDM in all women using a blood-based measure of circulating glucose to those from remaining studies. The finding of a weaker association in those with the universal blood test suggests that our concerns regarding confounding by indication may be valid. Whilst the harmonised binary variable can contain all data from all of the studies, we would recommend that other

pooled individual participant studies undertake similar subgroup analyses where different methods have been used to assess a harmonised variable.

A further challenge with data harmonisation is the loss of information through having to harmonise to the study with least detail for each measure, which could increase the risk of residual confounding. For example, in the present study maternal education was harmonised into three categories from the more granular detail available within many of the cohorts, and similarly maternal smoking in pregnancy was harmonised to yes versus no, when several studies had more detailed measures on amount and timing of smoking (e.g. if a women had smoked periconceptually and quit before pregnancy). Thus, the associations of GMD with offspring BMI might be influenced by residual confounding due to this 'lowest common denominator'. SEP might be expected to confound away from the null, but as smoking results in lower BMI [47], it might mask an association (confound towards the null). As there are many different measures across the studies for both maternal education and smoking, to explore the possible effect of this in subgroups would result in groups with small numbers for which robustly identifying between subgroup heterogeneity would be difficult and counter one of the key benefits of larger sample sizes.

Available analytic methods

A key opportunity of federated analysis is the ability to analyse data from multiple cohorts without the need for data transfer. This minimises the administrative burden of data transfer agreements and governance issues related to physical data sharing. In contrast to the traditional approach (where researchers from separate institutions run analyses which are then meta-analysed by a central group), the federated approach is more time efficient and flexible as one researcher can perform all analyses and combine results. However, a limitation with

DataSHIELD is that only a small subset of R packages are available so far, as any new packages need to be integrated and tested to ensure that disclosure risk is minimised.

Whilst many R packages are now implemented in DataSHIELD (e.g. Metafor) [48], at the time of analysis two methods were not available: multiple imputation and mixed effects models. In the absence of multiple imputation we used complete case analysis which in some scenarios carries the risk of bias [47]. To explore potential selection bias due to attrition and cohorts differentially contributing data to different analyses, we repeated analyses restricting to the subgroup of participants with data at the oldest age period. For analyses with maternal education as the exposure we found lower estimates in this subgroup at earlier ages which may suggest potential selection bias with results at the older age being underestimated. By contrast, for analyses with gestational diabetes as the exposures we found stronger estimates at earlier ages suggesting that estimates at older ages may be overestimated. Where complete case analysis is used, we therefore suggest that at at minimum authors fully describe missing data, consider its likely mechanisms and explore the potential for bias where possible.

The unavailability of mixed effects models meant that we were not able to explore associations with change in BMI as offspring aged in a way that accounted for correlation between repeat measures. Mixed effects models would also have enabled us to use all available data from participants with at least one measure of BMI, under a missing at random assumption [49, 50]. Notwithstanding, our results for example with maternal education are broadly similar to models which did use trajectory analysis, i.e. showing widening inequalities [12]. DataSHIELD is a continually evolving project, and the implementation of other new methods is underway.

Summary & future implications

In this multicohort study with 18 cohorts and up to 206,180 participants we have illustrated potential scientific gains of collaboration and data sharing between international birth cohorts. We have demonstrated how federated analysis using DataShield with cohorts from the ECCN provides opportunities to tackle research questions with increased statistical power and the ability to explore consistency (replication) across independent studies without the need to share data. We acknowledge and demonstrate the possibility of bias and residual confounding resulting from harmonising data across multiple cohorts and the limitations that result from federated data platforms, i.e. not having more advanced data analysis methods. Whilst we have focused here on DataShield, we expect that other federated analysis platforms will similarly focus on straightforward descriptive and generalised regression models as more advanced methods are added to the platform.

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Table 1: Summary of cohort characteristics

Cohort name	Country	City/area	Design	No. of included children	Birth year(s)	Age range of included children (years)
ABCD	Netherlands	Amsterdam	Prospective	6152	2003 - 2004	0 - 12
ALSPAC	United Kingdom	Greater Bristol	Prospective	10499	1991 - 1992	0 - 17
BiB	United Kingdom	Bradford	Prospective	13400	2007 - 2011	0 - 10
CHOP	Germany, Belgium, Italy, Poland, Spain	Munich, Nuremberg, Liege, Brussels, Milano, Warsaw, Reus, Tarragona	Prospective	1669	2002 - 2004	0 - 11
DNBC	Denmark	Greater Copenhagen	Prospective	77534	1996 - 2002	0 - 18
EDEN	France	Nancy & Poitiers	Prospective	1765	2003 - 2005	0 - 12
ELFE	France		Prospective	17926	2011	0 - 9
GECKO	Netherlands	Drenthe	Prospective	2748	2006 - 2007	0 - 11
Gen-R	Netherlands	Rotterdam	Prospective	8680	2002 - 2006	0 - 10
HGS	Greece	Attica, Etoloakarnania, Thessaloniki, Iraklion	Cross-sectional[a]	2570	1994 - 2000	10 - 14
INMA	Spain	Gipuzkoa, Sabadell, Valencia	Prospective	1918	2003 - 2008	0 - 11
MoBa	Norway		Prospective	85589	1999 - 2008	0 - 13
NFBC66	Finland		Prospective	7709	1966	0 - 16
NFBC86	Finland		Prospective	7315	1985 - 1986	0 - 16
NINFEA	Italy	Florence, Rome, Turin	Prospective	6532	2005 - 2016	0 - 14
Raine	Australia	Perth	Prospective	2548	1989 - 1992	1 - 17
Rhea	Greece	Crete	Prospective	1002	2007 - 2008	0 - 12
SWS	United Kingdom	Southampton	Prospective	3012	1998 - 2007	0 - 10

Abbreviations: ABCD, Amsterdam Born Children and their Development; HGS, Healthy Growth Study.

[a]Information on early life exposures collected retrospectively.

ORIGINAL UNEDITED MANUSCRIPT

Figure 1: Flow chart of cohorts and participants. Signed agreements received and DataSHIELD access credentials provided. Signed agreements received and DataSHIELD access credentials provided.

Figure 2: Exposure descriptive statistics
2a: Maternal education: dark blue = low education, teal = medium education, yellow = high education, orange = missing
2b: Normalised Difference Vegetation Index
2c: Gestational diabetes: dark blue = no pregnancy diabetes, teal = pregnancy diabetes, orange = missing

No data was available on gestational diabetes for CHOP as this was an exclusion criterion for entry into the study. For all other studies, figures are blank where the exposure is entirely missing. Values for NDVI represent median and interquartile range. NDVI = Normalised Difference Vegetation Index.

Figure 3: Associations between maternal education at birth and child BMI z-scores using one-stage IPD meta-analysis.
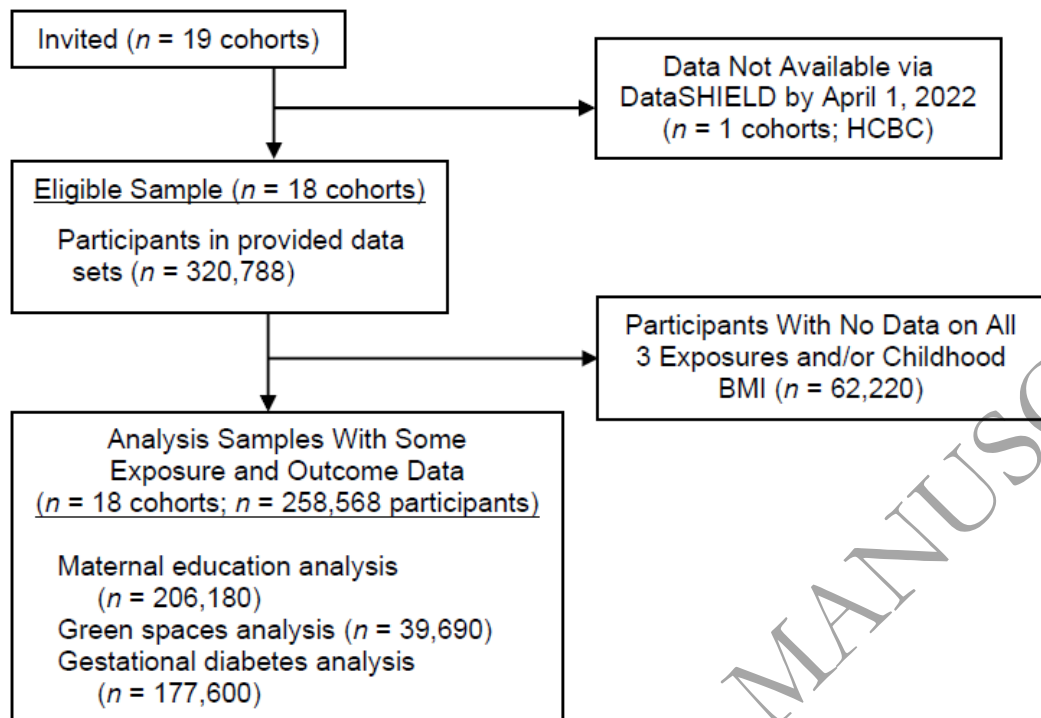Models adjusted for cohort, child sex and exact age at measurement in days. Solid fill = maximum available sample; no fill = restricted to sample with available data at ages 14-17.

Figure 4: Associations between Normalised Difference Vegetation Index in pregnancy and child BMI z-scores using one-stage IPD meta-analysis
Models adjusted for cohort, child sex, exact age at measurement, maternal education, parity and area deprivation. Normalised Difference Vegetation Index scaled by interquartile range. Solid fill = maximum available sample; no fill = restricted to sample with available data at ages 14-17. BMI = Body Mass Index.

Figure 5: Associations between gestational diabetes and child BMI z-scores using one-stage IPD meta-analysis
Models adjusted for cohort, child sex, exact age at measurement, maternal education, maternal age at birth, pre-pregnancy BMI, pregnancy smoking and parity. Solid fill = maximum available sample; no fill = restricted to sample with available data at ages 14-17. BMI = Body Mass Index.

```
Invited (n = 19 cohorts)
```

```
Data Not Available via
DataSHIELD by April 1, 2022
(n = 1 cohorts; HCBC)
```

```
Eligible Sample (n = 18 cohorts)
Participants in provided data
sets (n = 320,788)
```

```
Participants With No Data on All
3 Exposures and/or Childhood
BMI (n = 62,220)
```

```
Analysis Samples With Some
Exposure and Outcome Data
(n = 18 cohorts; n = 258,568 participants)

Maternal education analysis
   (n = 206,180)
Green spaces analysis (n = 39,690)
Gestational diabetes analysis
   (n = 177,600)
```
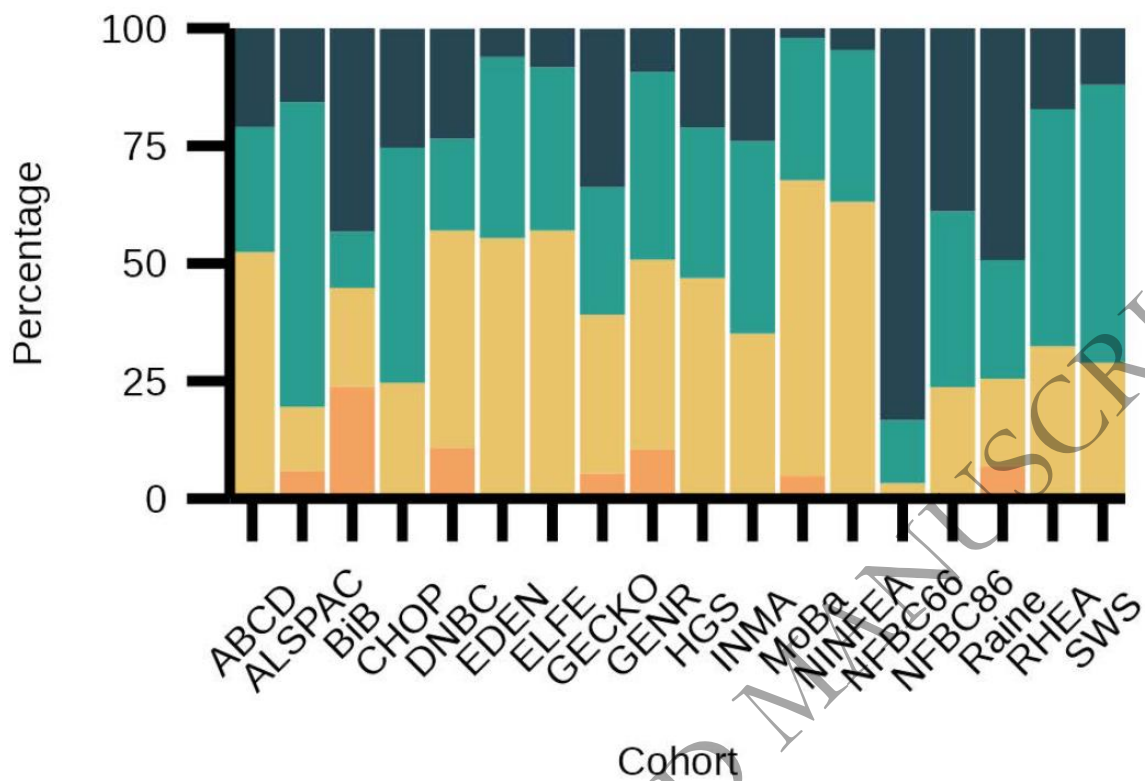
Age, years	Reference (high)	Exposed	No. of Studies		Estimate (95% CI)
Medium education					
0-1	105886	59454	17		0.01 (0.00, 0.02)
	3914	4737	5		0.02 (-0.02, 0.07)
2-3	47261	26551	16		-0.02 (-0.04,-0.01)
	1592	3283	4		-0.03 (-0.08, 0.03)
4-7	76650	41647	17		0.09 (0.08, 0.10)
	4336	7196	5		0.02 (-0.03, 0.06)
8-13	59502	33481	18		0.15 (0.13, 0.16)
	4622	8713	5		0.10 (0.05, 0.14)
14-17	6127	9938	5		0.10 (0.07, 0.14)
	6127	9938	5		0.10 (0.07, 0.14)
Low education					
0-1	105886	35220	17		0.02 (0.00, 0.03)
	3914	9077	5		0.04 (-0.00, 0.09)
2-3	47261	13017	16		0.03 (0.00, 0.05)
	1592	6342	4		-0.01 (-0.07, 0.05)
4-7	76650	28268	17		0.16 (0.14, 0.17)
	4336	9520	5		0.02 (-0.02, 0.07)
8-13	59502	24461	18		0.24 (0.22, 0.26)
	4622	9714	5		0.15 (0.10, 0.20)
14-17	6127	11188	5		0.20 (0.16, 0.23)
	6127	11188	5		0.20 (0.16, 0.23)

-0.50   0.00   0.50   1.00   1.50

Difference in Childhood BMI
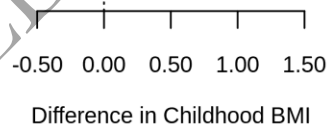
Age, years	No. of Participants	No. of Studies		Estimate (95% CI)
0-1	39,690	10		0.05 (0.03,0.06)
	1,166	2		-0.01 (-0.11,0.09)
2-3	22,658	9		0.02 (0.00,0.04)
	759	1		-0.02 (-0.14,0.09)
4-7	36,040	10		0.04 (0.02,0.05)
	4,005	2		0.01 (-0.06,0.08)
8-13	29,566	10		0.04 (0.01,0.06)
	6,313	2		0.04 (-0.01,0.10)
14-17	7,096	2		-0.00 (-0.04,0.04)
	7,096	2		-0.00 (-0.04,0.04)

-1.50   -1.00   -0.50   0.00   0.50   1.00

Difference in Childhood BMI

Age, years	Unexposed	Exposed	No. of Studies		Estimate (95% CI)
0-1	3135	3135	14		0.00 (-0.04,0.04)
	36	36	3		-0.03 (-0.30,0.23)
2-3	1384	1384	13		0.03 (-0.03,0.08)
	9	9	2		0.13 (-0.48,0.73)
4-7	2140	2140	14		0.01 (-0.03,0.06)
	34	34	3		0.18 (-0.10,0.46)
8-13	1117	1117	14		0.18 (0.12,0.25)
	65	65	3		0.28 (-0.01,0.58)
14-17	65	65	3		0.12 (-0.13,0.38)
	96	96	3		0.17 (-0.04,0.38)

-0.50   0.00   0.50   1.00

Difference in Childhood BMI