Maternal origin of children-onset asthma: evidence from observational study and instrumental variable analysis

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Research Article

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Abstract

Background

An inverse association was observed between birthweight and children-onset asthma (COA), the origin of the connection however remains elusive. Instrumental variable causal inference analysis can be used to reveal the origin of such associationbut requires resolving the mixed genetic effect of birthweight into fetal/maternal-specific components.

Methods

We first performed a meta-analysis to study the relation between birthweight and COA using updated literature published from 2014 to 2020. Using maternal-specific instruments of birthweight, we next performed a genetic risk score (GRS) based Mendelian randomization (MR) to estimate the causal effect of low birthweight on COA in mother-offspring pairs (n=3,634) and father-offspring pairs (n=1,334) of the UK Biobank. Two sensitivity analyses of MR were applied to assess the robustness of our causal inference and another method called iMAP was conducted to offer complementary result regarding the direction of referred causality.

Results

The updated meta-analysis indicated individuals born with lower birthweight would be more vulnerable to asthma in childhood. The GRS-based MR analysis demonstrated a significantly negative maternal impact of birthweight on COA (β=-0.162, P=0.037) after adjusting for offspring's genetic effect in mother-offspring pairs, but failed to repeat this relation in father-offspring pairs. Our sensitivity analyses showed such inverse association was robust against horizontal pleiotropy of used instruments (β=-0.169, P=0.030) and was not likely affected by preterm birth (β=-0.165, P=0.035). The iMAPresult also provided additional evidence supporting the causal influence of low birthweight on COA.

Conclusions

This study provides supportive evidence for the maternal origin of COA and helps guide early prevention for COA via improving intrauterine environments during pregnancy.

Implications And Contribution

By performing a genetic risk score based Mendelian randomization analysis, we estimated the causal effect of birthweight on children-onset asthma (COA) in parent-offspring pairs of the UK Biobank cohort using maternal-specific instruments of birthweight. We discovered substantial evidence for the causal relationship between birthweight and COA in mother-offspring pairs, supporting the maternal origin of COA. From a methodological perspective, our work offered a successfully empirical example to infer the causal association between an intrauterine environmental exposure and an offspring outcome by examining the association between maternal genotypes related to offspring birthweight and offspring outcome while conditioning on offspring genotype at the same set of genetic variant instruments.

Background

Asthma is one of the most common chronic pediatric diseases characterized by chronic airway inflammation associated with airway hyperresponsiveness; it affects one in three children during the first three years of life, and happens more often on younger children (Nurmagambetov, et al., 2018). The last thirty years have witnessed a stunningly elevated incidence of children-onset asthma (COA) in most developed counties, with the prevalence of severe COA increasing up to 5% in asthma patients, although not each of these children remain this disease in later age. COA imposes a great economic burden on global society continuously in its wake (Fitzmaurice, et al., 2019); therefore, it is critical to understand the etiology, inducement, and development of COA for early prevention.

Besides familial history (Litonjua, et al., 1998) and genetic foundation (Ferreira, et al., 2019), epidemiological studies have discovered that both allergic and non-allergic triggers contribute to the development of asthma. However, established risk factors cannot completely explain the occurrence pattern of COA. As another appealing interpretation of disease risk, the causal role of perinatal intrauterine environments in COA has garnered widespread interest. Due to the difficulty of prospectively measuring in-utero exposures accurately, birthweight is widely used as a surrogate variable for early life development in practice and has long been hypothesized to exert a lasting influence on individual's predisposition to the risk of many diseases in later life including asthma — a more generalized hypothesis referred to as the developmental origins of health and disease (DOHaD) or the Barker hypothesis of adult diseases (Duijts, 2012).

According to a systematic review of eighteen studies covering from 1966 to 2013 (Mu, et al., 2014), there was an increase of 34% (95% confidence intervals (CIs) 13–60%) in COA risk for individuals with lower birthweight compared to normal ones; this finding was further supported by other studies (Mebrahtu, et al., 2015; Xu, et al., 2014). Nevertheless, it is currently hard to make a conclusive causality between adverse intrauterine environments (approximated by low birthweight) and the risk of COA under the DOHaD framework because birthweight is a special exposure proxy genetically affected by both maternal and fetal genomes and represents a combined outcome of maternal and fetal factors (Warrington, et al., 2019).

Genetic analysis with birthweight-relevant instrumental variable causal inference offers an efficient solution for this challenging problem, but it requires first resolving the mixed genetic effect of birthweight into fetal-specific and maternal-specific components, which is the key to elucidate the origin of observed association between birthweight and COA (Fig. 1). In terms of the interpretations given in this figure and the core of DOHaD, the maternal-specific component

can be employed to characterize the causal relation between birthweight and COA (Moen, et al., 2020; Zhang, et al., 2022). Maternal/fetal-specific summary statistics of single nucleotide polymorphisms (SNPs) on birthweight were recently released (Warrington, et al., 2019), providing us an unprecedented opportunity to assess the intrauterine effect by elaborating the maternal contribution of birthweight to COA.

We first performed a meta-analysis to study the relation between birthweight and COA using updated literature published from 2014 to 2020. To evaluate the causal role of birthweight in COA using maternal-specific birthweight instruments, we next analyzed parent-offspring pairs (n = 4,968) of the UK Biobank cohort (Bycroft, et al., 2018) and conducted a genetic risk score (GRS) analysis (D'Urso, et al., 2021; Moen, et al., 2020; Tyrrell, et al., 2016) under the Mendelian randomization (MR) framework. As a complementary approach to the GRS-based MR, another method called iMAP (Zeng, et al., 2018) was carried out to assess the direction of causality between maternal-specific birthweight and COA.

Materials And Methods

Updated literature for meta-analysis

Literature searching strategy

We first performed a literature retrieval mainly on PubMed from January 2014 to December 2020 for searching articles on the relationship between birthweight (and related factors including premature birth and fetal development) and COA. We made no restriction on study designs and considered both cohort and population-based studies, but limited articles in English. With the guideline of PRISMA (Moher, et al., 2009), we applied the following search command: ("birthweight" or "BW" or "low birthweight" or "LBW" or "premature birth" or "infant-low birthweight" or "birthweight" or "Birthweight" or "Birthweight" or "fetal growth retardation" or "intrauterine growth restriction" or "intrauterine growth retardation" or "fetal development" or "small for gestational age") and ("asthma" or "Asthma" or "wheezing" or "Respiratory Illness") not ("animal") ("2014/01/01" [Date - Publication]: "2020/12/30" [Date - Publication]).

Exclusion criteria, data extraction and meta-analysis

A total of 644 articles (633 articles by searching and additional 11 articles by references scanning) were originally obtained (Fig. 2). The exclusion criteria for articles filtering included: (i) the title and abstract did not contain any information on birthweight and/or asthma; (ii) insufficient results were available on birthweight and asthma; (iii) duplicated studies on the same topic; (iv) review, letter-to-editor, response, or commentary articles; (v) articles were about clinical drug trials for asthma; and (vi) articles were already incorporated in previous systematic reviews; (vii) birthweight was discretized with the same threshold in these articles. Finally, a total of 12 studies (15 association results) published after 2014 were included.

For each included study, we extracted some key information such as total sample size, criteria for low birthweight, study population as well as effect (odds ratio (OR) or risk ratio (RR)) and its 95% confidence intervals (CIs). Then, we reserved the studies which adopted the most common standards for low birthweight and applied a weighted meta-analysis method to estimate the combined effect of birthweight on COA. We used the Cochran's Q test to examine the effect heterogeneity among incorporated studies (Thompson and Sharp, 1999).

Genetic Risk Score Based Instrumental Variable Causal Inference

Parent-offspring pairs in the UK Biobank cohort

We applied the parent-offspring UK Biobank data (Bycroft, et al., 2018) to perform the GRS analysis for examining the causal influence of birthweight (as a proxy of intrauterine environment exposures) on COA while accounting for confounding effect of offspring's genetic background (Moen, et al., 2020). To obtain parent-offspring pairs in the UK Biobank cohort, we calculated the kinship coefficient for all participants in the UK Biobank via the KING software and identified 4,968 independent parent-offspring pairs of European ancestry, including 1,334 father-offspring pairs and 3,634 mother-offspring pairs. To be consistent with the analyses above, we defined COA cases in terms of the diagnosis age (< 19 years old) (Ferreira, et al., 2019) for any offspring suffering from asthma diagnosed by doctor, and obtained 314 and 96 COA cases in mother-offspring pairs and father-offspring pairs, respectively.

Birthweight-related instrumental variable selection

When constructing GRS (i.e., g_1 and g_2) we selected SNPs with maternal-only effects ($I^2 < 0.1$ and $P < 6.6\times10^{-9}$) (Warrington, et al., 2019) serving as instrumental variables for birthweight in terms of confidence intervals around the maternal/fetal-specific effects estimated with structural equation model (Warrington, et al., 2018). The fetal-specific SNP effect was calculated conditioning on mother's genotypes and the maternal-specific SNP effect was calculated conditioning on offspring's genotypes, with 297,356 European individuals with their own birthweight and 210,248 European individuals with offspring birthweight. The selected instruments included 15 SNPs with directionally-opposing maternal and fetal effects, 26 SNPs with directionally-concordant maternal and fetal effects, and 31 SNPs with maternal-only effects (Warrington, et al., 2019; Zhang, et al., 2022).

Logistic model for GRS of parent-offspring pairs

Four directed acyclic graphs, which illustrates how maternal genotypes influence offspring birthweight and COA, are shown in Fig. 3. Based on the illustration, to assess the causal association of low birthweight on COA, we built a logistic model for mother-offspring pairs

$$logit\,(\pi) = \mathbf{X}\alpha + g_1\beta + g_2\theta$$

where π = $E(y)$ with y an indicator variable of COA, $\mathbf{X}$ indicated the design matrix of covariates with α the effect vector, $g_1=\sum_j^J G_{1j}$ and $g_2=\sum_j^J G_{2j}$ indicated maternal or offspring's GRS, where G_{1j} and G_{2j} were the genotypes of maternal-specific SNP instruments associated with birthweight (Warrington, et al., 2019), with β and θ the corresponding effects. Analogous to (Moen, et al., 2020), we constructed an unweighted GRS by adding the expected number of increasing-birthweight alleles together.

We primarily incorporated sex of offspring as the covariate as well as an intercept term, and standardized both g_1 and g_2. Our objective was to examine H_0: $\beta = 0$ to assess whether there was evidence supporting the maternal-specific birthweight effect on COA after conditioning on fetal genotypes. The similar logistic analysis using the same set of SNP instruments with only maternal-specific impact was conducted in father-offspring pairs to assess whether there was evidence for the postnatal environmental effect (genetic nurture or dynastic effects) on COA through birthweight while adjusting for fetal genotypes (Moen, et al., 2020).

Sensitivity analysis of the GRS-based MR

As shown in prior literature (D'Urso, et al., 2021; Moen, et al., 2020), the GRS-based MR could provide important implication regarding causality as long as the three critical modeling assumptions (i.e., the relevance assumption, the independence assumption, and the exclusion restriction assumption) are satisfied. Particularly, to protect against horizontal pleiotropy of instruments required by the exclusion restriction assumption, in terms of the GWAS Catalog (https://www.ebi.ac.uk/gwas) we excluded several birthweight SNP instruments which were associated with some important COA-related risk factors (e.g., body mass index and smoking). The remaining instruments were used to construct the GRS and then the same analysis was implemented.

Gestational duration is highly correlated with birthweight, and should be considered when analyzing birthweight. However, the information of gestational duration was unavailable from the UK Biobank cohort. To examine the impact of likely premature birth (Warrington, et al., 2019), we performed another sensitivity analysis focusing only on parent-offspring pairs in which offspring had a normal measurement of birthweight (< 2.5kg and > 4.5kg).

Causal Direction By The Imap Analysis

To complement the GRS-based MR, we carried out another analysis called iMAP (Zeng, et al., 2018) with the hope of yielding additional evidence with regards to the causal relation between low birthweight and COA. Compared to existing methods such as GPA (Chung, et al., 2014) and GWAS-pw (Pickrell, et al., 2016), iMAP has the advantage of accounting for un-independence due to phenotypic correlation or sample overlap. Briefly, iMAP estimates the probability of SNPs related to one phenotype that is also associated with the other. By calculating such probability, iMAP has the potential to offer suggestion for directional causality between birthweight and COA.

Analogous to iMAP, an alternative methods called latent causal variable (LCV) model could be also applied to distinguish genetic correlation from causation between birthweight and COA by calculating the posterior causality proportion (GCP) (O'Connor and Price, 2018). The magnitude of GCP could be employed to evaluate the likelihood that there existed evidence for a causal influence of birthweight on COA and the sign of GCP could be applied to infer the potential causal direction between birthweight and COA. However, we obtained a non-significant genetic correlation estimate between them ($P > 0.05$) (Bulik-Sullivan, et al., 2015), which would make the result of LCV meaningless and inaccurate; thus, we did not pursue LCV further.

The summary statistics of birthweight were available from (Warrington, et al., 2019); the summary statistics of COA were obtained from (Ferreira, et al., 2019) which analyzed 314,633 European individuals (including 13,962 cases with age less than 19 years old). For both summary statistics of birthweight and COA, we performed the similar quality control for common SNPs (minor allele frequency > 0.01) as done in (Bulik-Sullivan, et al., 2015).

Results

Finding in previous studies and combined result of meta-analysis

In terms of our literature retrieval, we reserved a total of 18 results, including 3 multi-nations meta-studies covering from 1966 to 2013 and 15 new studies published between 2014 and 2020. Among those studies, six were performed on individuals of European ancestry, and almost all demonstrated that low birthweight was a strong risk factor of COA regardless of ancestral groups (Table 1).

We first performed meta-analysis among the recent 15 results and then combined the result with each of the prior three reviews. As the definition of low/high birthweight was slightly different across studies, only 12 out of 15 studies with the threshold of 2.5kg were incorporated in our meta-analysis. Because of the heterogeneity in effects among these included studies (the Cochran's $P < 0.01$), we here primarily reported random-effects meta-analysis results. In terms of studies collected between 2014 and 2020, the risk of COA for individuals with lower birthweight increased by 68% (95% CIs 47 ~ 92%) (Fig. 4).

The leave-one-out sensitivity analysis indicated no single study could substantially change the pooled estimated effect (Figure S1). Such inverse relation also held if including these prior meta-studies (OR = 1.51, 95% CIs 1.37 ~ 1.65) and were robust in stratification analyses of distinct birthweight threshold (Figure S2), study population (Figure S3), study design (Figure S4), and exposure and outcome ascertainment (Figures S5-S6), although sometimes the heterogeneity remained. In summary, based on the results of meta-analysis, we concluded there was a negative association between birthweight and COA, implying that individuals born with lower birthweight would be more vulnerable to asthma in childhood.

Table 1
Summary information of studies investigating the relationship between birthweight and childhood-onset asthma

id	country or region	Total number	OR/RR (95%CIs)	cutoff for birthweight (kg)	Study Design	Age at follow up	Number in each group	Outcome ascertainment	Exposure ascertainment	Quality Score	race	Ref
A	Europe	1,105,703	1.16 (1.13–1.20)	< 2.5 and > 2.5								(Xu 201
B	Europe	30,877	1.28 (1.09–1.50)	< 2.5 and > 2.5								(Mu 201
B	Europe	30,877	1.34 (1.13–1.60)	< 2.5 and 2.5-4.0								(Mu 201
C	Europe	1,712,737	1.37 (1.05–1.79)	< 2.5 and 2.5-4.0								(Me et a 201
C	Europe	1,712,737	1.60 (1.39–1.85)	< 2.5 and > 2.5								(Me et a 201
1	Brazil	1,534	1.38 (1.05–1.81)	< 2.5 and > 2.5	PC	< 4	310 vs. 989	a, b	a	7	mixed	(Re 201
2	Spain	766	1.71 (1.06–2.76)	< 2.5 and 2.5-4.0	RC	< 1	149 vs. 617	a, b	a, b	8	Spain	(Pé Yar al.,
3	UK	13,734	1.29 (1.12–1.50)	2.5-4 and > 4.0	PC	0–7	1,139 vs. 11,341	a, b	a, b	8	mixed	(Me et a 201
3	UK	13,734	0.91(0.79–1.04)	< 2.5 and > 2.5	PC	0–7	11,341 vs. 1,254	a, b	a, b	8	mixed	(Me et a 201
3	UK	13,734	1.60 (1.05–1.79)	2.0-2.5 and > 2.5	PC	0–7	1,139 vs. 12,595	a, b	a, b	8	mixed	(Me et a 201
4	USA	680	5.20 (2.80–8.70)	< 2.0 and > 2.5	RC	6–17	251 vs. 293	a, b	a	7	mixed	(Jo et a 201
4	USA	680	8.80 (4.60–14.9)	< 2.5 and 2.5–3.5	RC	6–17	136 vs. 293	a, b	a	7	mixed	(Jo et a 201
5	Iran	3,102	1.32 (0.97–1.80)	< 2.5 and 2.5–3.5	RC	6–7	269 vs. 1,165	a	a	6	Caucasian	(Ra al.,
		3,554	1.52 (1.04–2.22)	< 2.5 and > 2.5	RC	13–14	382 vs. 1,104	a	a	6	Caucasian	Rah al.,
6	Australia	2,775	1.75 (1.07–2.87)	< 2.5 and > 2.5	RC	7	299 vs. 2,461	a	b	7	Tasmanian	(Ma et a 201
		2,775	2 (1.03–3.87)	< 2.5 and > 2.5	RC	12	136 vs. 2,381	a	b	7	Tasmanian	(Ma et a 201
7	USA	90,721	1.43 (1.25–1.63)	< 3.0 and > 3.0	RC	0–17	8,202 vs. 82,519	a	a	7	mixed	(Zh al.,
8	Italy	80	10.30 (1.50–27.5)	< 2.5 and > 2.5	PC	2.8–8.8	-	a	b	8	Italian	(Bo al.,
9	Brazil	375	2.90 (1.70–4.90)	< 2.5 and > 2.5	RC	13–14	-	a	a	8	mixed	(Fe et a 201

Note: A-C were three previous review paper, 1–15 were results of studies published between 2014–2020; the studies in green were included in our meta-analy questionnaire, b = hospital records; PC: prospective cohort, RC: retrospective cohort.

id	country or region	Total number	OR/RR (95%CIs)	cutoff for birthweight (kg)	Study Design	Age at follow up	Number in each group	Outcome ascertainment	Exposure ascertainment	Quality Score	race	Ref
10	China	701	1.75 (1.11–2.75)	< 2.5 and 2.5-4.0	RC	0–1	-	b	b	6	Asian	(Yi 201
11	Japan	6364	1.22 (0.89–1.65)	2.5-4 and > 4.0	RC	3	560 vs. 5,756	a	a	7	Asian	(Ta al.,
		6364	0.53 (0.09–1.71)	0.5-1 and > 2.0	RC	3	5,756 vs. 48	a	a	7	Asian	Tak al.,
12	Brazil	445	2.38 (1.33–4.27)	1-1.5 and > 2.0	RC	1–5	80 vs. 160	a	a	6	mixed	(Sir al.,
12	Brazil	445	1.52 (0.88–2.63)	1.5-2 and > 2.0	RC	1–5	114 vs. 160	a	a	6	mixed	(Sir al.,
12	Brazil	445	1.02 (0.55–1.90)	< 2.5 and > 2.5	RC	1–5	90 vs. 160	a	a	6	mixed	(Sir al.,
13	China	628,878	1.14 (1.10–1.19)	< 2.5 and > 2.5	RC	0–6	40,704 vs. 588,174	b	b	6	Asian	(Lir 201
14	Iraq	952	16.70 (6.97–37.49)	< 2.5 and > 2.5	RC	4.2–9.2	273 vs. 679	b	b	6	Arabian	(Al et a 201
15	Japan	45,060	1.14 (1.03–1.26)	< 2.5 and > 2.5	RC	0.5–10	-	a	a	7	Asian	(Fu et a 202

Note: A-C were three previous review paper, 1–15 were results of studies published between 2014–2020; the studies in green were included in our meta-analy questionnaire, b = hospital records; PC: prospective cohort, RC: retrospective cohort.

Association between birthweight and COA in the full UK Biobank cohort

We here examined the relation between birthweight and COA among all available participants in the full UK Biobank cohort. It was discovered the estimated effect=-0.205 (se = 0.038, P = 5.12×10^{-8}) for birthweight and 0.175 (se = 0.038, P = 4.51×10^{-6}) for squared birthweight.

Estimated causal association between birthweight and COA

Furthermore, we carried out logistic model using the mother-offspring or father-offspring datasets, respectively. Using all birthweight-associated instruments, we identified that the maternal GRS was negatively related to COA (β=-0.162, P = 0.037) after adjusting for sex and offspring's genetic impact in mother-offspring pairs (Table 2). However, we did not find significant associations between the paternal GRS and COA in father-offspring pairs, and failed to detect substantial relation between the fetal GRS and COA in mother-offspring or father-offspring pairs.

Table 2
Association between parental/fetal GRS and COA after conditioning on offspring genotypes in parent-offspring pairs calculated with selected SNP instruments of birthweight

COA	parental GRS		fetal GRS	
	β (se)	*P*	*β (se)*	*P*
maternal GRS (cases vs. control)				
A (3320 vs. 314)	-0.162 (0.078)	0.037	-0.127 (0.078)	0.103
B (3320 vs. 314)	-0.169 (0.078)	0.030	-0.128 (0.078)	0.101
C (3299 vs. 310)	-0.165 (0.079)	0.035	-0.135 (0.078)	0.086
paternal GRS (cases vs. control)				
A (1238 vs. 96)	-0.067 (0.141)	0.632	0.038 (0.141)	0.785
B (1238 vs. 96)	0.039 (0.139)	0.778	-0.025 (0.141)	0.858
C (1196 vs. 91)	0.037 (0.144)	0.801	-0.051 (0.145)	0.723

Note: A = the GRS analysis with all available instruments; B = the GRS analysis with some instruments with potentially horizontal pleiotropic effects removed; C = the GRS analysis analyzing only offspring with normal birthweight.

Results of sensitivity analyses

After excluding several instruments with potentially horizontal pleiotropic effects, we found this inverse relation was still substantial (β=-0.169, P = 0.030). We discovered the causal association between the maternal GRS and COA remained significant when only analyzing offspring with normal birthweight (β=-0.165, P = 0.035), indicating that our finding was less likely affected by preterm birth and that the detected causal connection might be not driven by offspring born at the extremes of birthweight.

Results for iMAP

In terms of the iMAP results, the probability of SNPs related to maternal-specific birthweight that were also associated with COA was 57.9%. In contrast, the probability of SNPs related to COA that were also associated with maternal-specific birthweight was only 22.4%. The two asymmetrical probabilities implied birthweight-associated loci were more likely related to COA than the other way around. Therefore, the result of iMAP provided us additional genome-wide evidence supporting the causal influence of birthweight on COA.

Discussion

In the present study, we first conducted a literature-updated meta-analysis from 2014–2020 and discovered birthweight had an inverse impact on COA in recent observational studies, consistent with the finding observed in the literature before 2014 (Mebrahtu, et al., 2015; Mu, et al., 2014; Xu, et al., 2014). Furthermore, we carried out the GRS analysis separately in the mother-offspring and father-offspring data. Together with our iMAP results, we found significant evidence in favor of the maternal influence of birthweight on COA, implying the intrauterine environments might play an important role in the development of COA.

Comparison to previous studies

Compared to prior studies (Zeng, et al., 2019; Zeng and Zhou, 2019), one of the greatest advantages for our work was its ability to isolate the relatively maternal and fetal contributions to birthweight (Warrington, et al., 2018) that rendered us the capability to investigate the origin of this observed relationship between low birthweight and COA. As the fetal and maternal effects of birthweight were remarkably distinct in direction and magnitude, ignoring such information not only limited the practical interpretation of prior findings, but also likely resulted in misleading findings. Therefore, our results provided a much clearer insight into the association between birthweight and COA, and had the potential to understand internal mechanisms in a deeper level.

Importance of the use of maternal-specific instruments

Several previous MR studies (Au Yeung, et al., 2016; Wang, et al., 2016; Zanetti, et al., 2018; Zeng, et al., 2019; Zeng and Zhou, 2019), which naively applied the fetal-specific instruments of birthweight to address the DOHaD hypothesis, were likely invalid when inferring the causal association between birthweight and adult diseases because of two reasons. First, the DOHaD hypothesis proposes an adverse intrauterine exposure leads to low birthweight and adult disease through developmental compensations, which contrasts with the assumption that birthweight itself displays a direct causal impact on disease. Thus, the nature of DOHaD requires us to employ the birthweight-related instruments with maternal-specific effect when seeking to uncover the causal association between an early exposure in life course or an intrauterine factor and an adult outcome of interest.

Second, the fetal genotype is highly correlated maternal genotype ($r \approx 0.50$) that influences offspring birthweight and also possibly has an impact on offspring health outcome (Warrington, et al., 2018). Any causal association discovered by using fetal-specific SNP instruments would also imply an indirect influence of mother; this violates the independence modeling assumption of MR study, where it requires the used instruments are not related to any confounders in the pathway from the exposure to the outcome under consideration.

Due to these complex situations, the standard MR analysis is infeasible when examining the DOHaD hypothesis. In contrast, recent studies (D'Urso, et al., 2021; Evans, et al., 2019; Moen, et al., 2020) have successfully demonstrated the GRS-based MR method, which determines the association between maternal genotypes related to offspring birthweight and offspring outcome while conditioning on offspring genotype at the same set of SNP instruments, is a valid strategy to estimate the causal effect.

Further research directions and limitations

Some limitations of this study need be mentioned. First, because of limited COA cases in parent-offspring pairs, we could not carry out stratified GRS analysis in terms of offspring's sex although prior studies showed significant sex difference in the risk of COA (Bao, et al., 2017). Second, like any MR studies, the validity of our causal inference depended on several critical modeling assumptions of MR, some of which are not completely testable in practice. For instance, due to unknown biological functions of these used birthweight-related SNP instruments, we cannot fully check the exclusion restriction assumption even though we performed a sensitivity analysis to assess such assumption.

Third, because some SNP instruments that are most strongly associated with birthweight might also show the strongest influence on offspring outcome (D'Urso, et al., 2021; Warrington, et al., 2019), which not only violates the exclusion restriction assumption of MR study but also violates the InSIDE assumption of MR-Egger regression (Bowden, et al., 2015). We cannot further conduct robust methods analogous to MR-Egger regression to evaluate and control horizontal pleiotropy. It is currently unknown how to carry out a formal test for evaluating horizontal pleiotropy and yield unbiased estimates of the causal effect under our GRS-based MR context.

Fourth, we recognized that the GRS-based MR analysis cannot completely rule out all confounders even though MR is less susceptible to confounding effects compared to other study designs (Davey Smith and Ebrahim, 2003). For example, low birthweight of offspring and higher risk of COA are likely due to common environments and lifestyles such as low socio-economic status, poor family income, polluted environment, and poor diet shared by parents and offspring, which result in the co-occurrence of low birthweight and high risk of COA. Thus, the causal association suggested in our work possibly in part results from residual confounders and should be thus interpreted with caution.

Finally, from a methodological perspective, despite the simplicity and effectiveness of the GRS-based MR, it requires genotypes and phenotypes for parent-offspring pairs with sufficient samples; such well-established cohorts and datasets are however not always available. There exist other causal inference methods (e.g., MR using maternal instruments only on non-transmitted alleles (Zhang, et al., 2015)) that were recently developed particularly for within-family MR studies (Brumpton, et al., 2020; Davies, et al., 2019; Gage, et al., 2016; Lawlor, et al., 2017), the empirical performance of these methods with the GRS-based MR approach is not comprehensively evaluated. The application of those methods to our objective is warranted to offer additional results for more robust conclusions.

Conclusion

Our study is among the first effort to unveil the relation between low birthweight and COA from an instrumental variable based causal inference perspective, and provides supportive evidence for the maternal origin hypothesis of COA. The finding helps guide early prevention for COA.

Abbreviations

COA	Children-onset asthma
GRS	genetic risk score
DOHAD	developmental origins of health and disease
MR	Mendelian randomization
PC	prospective cohort
RC	retrospective cohort
LCV	latent causal variable
SNPs	single nucleotide polymorphisms

Declarations

Ethics approval and consent to participate

The UK Biobank had approval from the North West Multi-Centre Research Ethics Committee (MREC) as a Research Tissue Bank (RTB) approval. All participants provided written informed consent before enrolment in the study, which was conducted in accordance with the Declaration of Helsinki. This approval means that other researchers do not require separate ethical clearance and can operate under the RTB approval.

Consent for publication

Not applicable.

Availability of data and materials

This study used the UK Biobank resource with the application ID 88159. Researchers can access to the UK Biobank dataset by applying to the UK Biobank official website (https://www.ukbiobank.ac.uk/).

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors Contributions

PZ and TW conceived the idea for the study. PZ obtained the data. PZ, TG, and SJ cleared up the datasets. SZ, SJ, and YW performed the data analyses. PZ, SZ, YW, YL, TW, and SJ interpreted the results of the data analyses. PZ, YW, and SJ wrote the manuscript with the participation of other authors.

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Figures

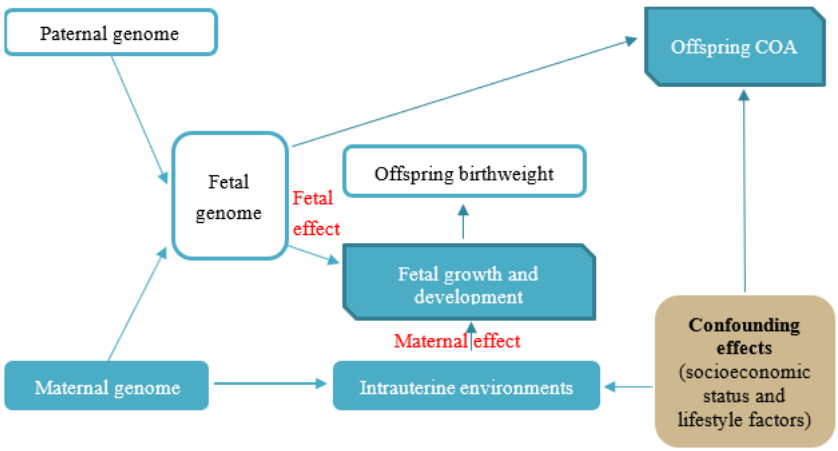

Figure 1

Framework for exploring the relation between birthweight and offspring COA.The key is to resolve the fetal/maternal-specific genetic effects of SNPs that were associated with birthweight when using birthweight as the proxy of maternal environments. Under the hypothesisof the developmental origins of COA, low birthweight caused by maternal adverse in-utero environmental factors (i.e., maternal-specific component of birthweight) reflects growth restriction which is assumed to further affect asthma in children, indicating the causal effect of fetal growth due to adverse maternal environments on offspring asthma. Fetal own genome is likely be a common genetic factor for low weight at birth (i.e., fetal-specific component of birthweight) and COA, indicating the genetic pleiotropy between birthweight and offspring outcome.

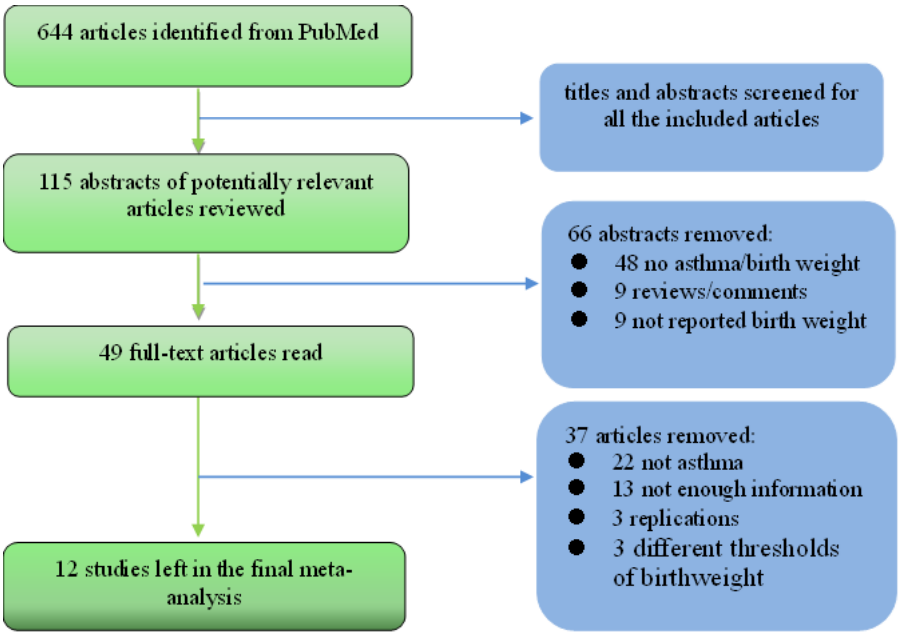

Figure 2

Flowchart of the study selection for investigating the association between lower birthweight and the risk of children-onset asthma.

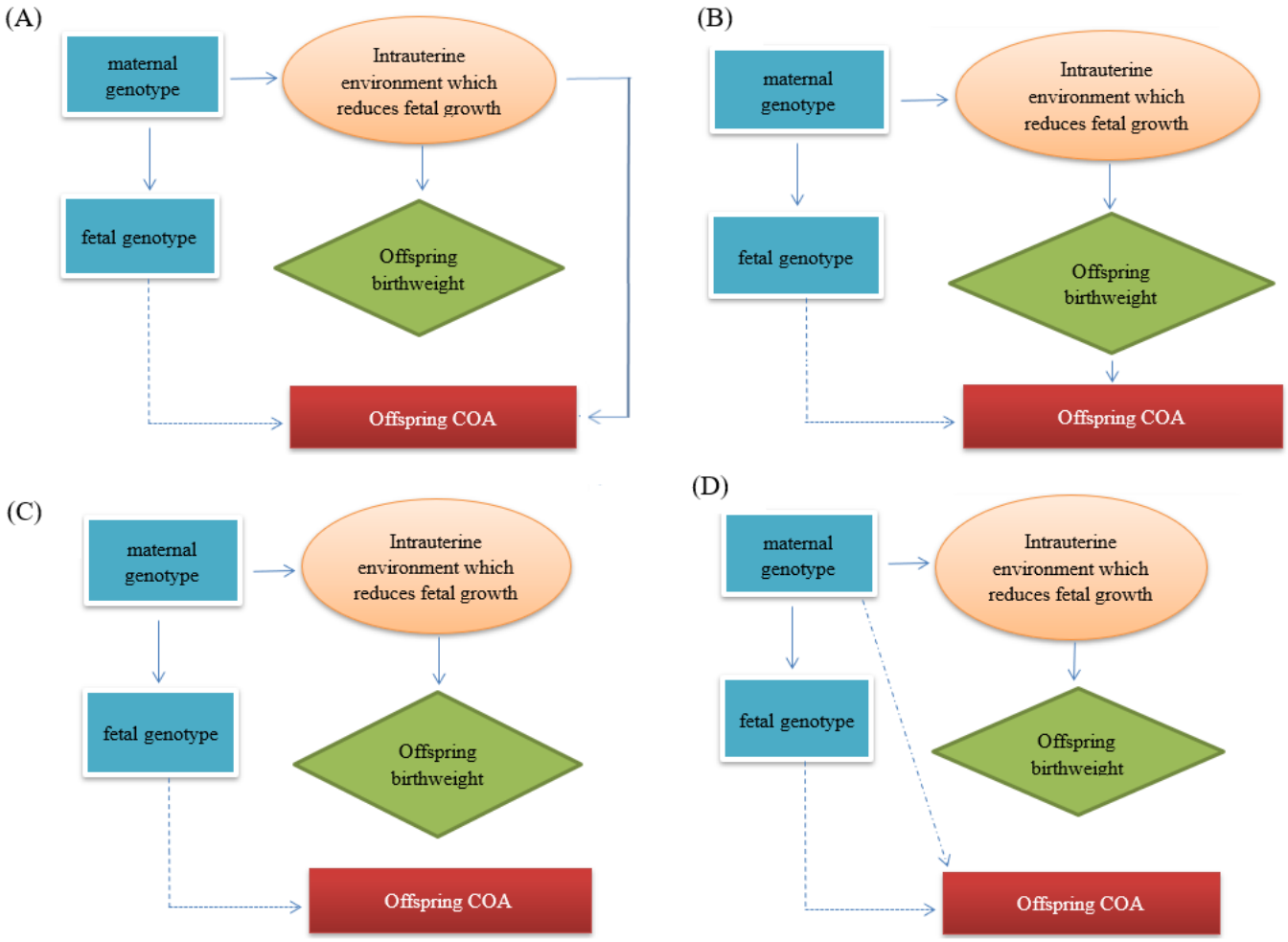

Figure 3

Four directed acyclic graphs in which maternal genotypes have a substantial influence on offspring birthweight and COA. (A) Maternal genotypes lead to an adverse intrauterine environment, which results in low offspring birthweight due to fetal growth restriction and subsequently developmental compensation that leads to increased risk of offspring COA. (B) Maternal genotypes lead to an adverse intrauterine environment that results in fetal growth restriction and low offspring birthweight, which is in turn causally related to increased risk of offspring COA. (C) Maternal genotypes lead to an adverse intrauterine environment, which results in fetal growth restriction and reduced birthweight; the same alleles of genotypes are transmitted to offspring and pleiotropically influence offspring COA through the offspring genome. (D) Maternal genotypes lead to an adverse intrauterine environment, which results to fetal growth restriction and reduced offspring birthweight; genotypes with maternal effects on offspring birthweight also pleiotropically influence offspring COA through the postnatal environment. The dotted line indicates the pathway in which the maternal genotype is related to offspring outcome is not involved in intrauterine growth restriction.

Supplementary Files

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