




Placental weight as a predictor of future health: Insights from a large-scale genome-wide association study

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ABSTRACT

Introduction: Placental weight has been associated with various adult-onset diseases, but the causal relationships and underlying mechanisms remain unclear.

Methods: This two-sample Mendelian randomization (MR) study utilized genome-wide association study (GWAS) data from multiple independent cohorts, primarily of European ancestry. The analysis included over 1.8 million individuals for type 2 diabetes mellitus (T2DM) outcomes. Data from four independent cohorts were used for validation. The inverse variance-weighted method was used for primary analysis, with weighted median, weighted mode, and MR-Egger regression for sensitivity analyses.

Results: Each standard deviation increase in genetically predicted placental weight was associated with T2DM ($\beta = -0.109$, 95 % CI: -0.184 to -0.034), basal cell carcinoma ($\beta = 0.130$, 95 % CI: 0.016 to 0.245), acute upper respiratory infections ($\beta = -0.062$, 95 % CI: -0.113 to -0.011), neurological diseases ($\beta = -0.009$, 95 % CI: -0.014 to -0.003), and endometrial cancer ($\beta = -0.561$, 95 % CI: -0.961 to -0.161). Placental weight also showed significant negative associations with blood glucose levels ($\beta = -0.102$, 95 % CI: -0.200 to -0.004). Mediation analyses revealed that dried fruit intake mediated 14.68 % of the total effect on T2DM risk, while immune cell phenotype analysis identified HLA DR on CD33dim HLA DR + CD11b + as a potential mediator in the causal pathway.

Conclusion: This study provides genetic evidence for a causal relationship between placental weight and T2DM risk, mediated partly through dietary habits and immune pathways. These findings suggest that early-life placental development may influence long-term metabolic health, highlighting the importance of prenatal care in preventing adult-onset diseases.

1. Introduction

The Developmental Origins of Health and Disease (DOHaD) theory emphasizes the significant influence of early-life environments on long-term health outcomes [1]. This aligns with the World Health Organization's life course approach, highlighting early-life factors' role in future health [2]. The placenta, crucial in the mother-fetus interface, not only facilitates nutrient and gas exchange but also acts as an endocrine organ regulating fetal growth and immune tolerance [3]. Placental

weight serves as a proxy for intrauterine environmental conditions and has been linked to long-term health trajectories [4].

Observational studies have suggested links between placental weight and adult-onset diseases, such as cardiovascular conditions and metabolic syndrome [5,6]. However, the precise causal relationships remain unclear due to limitations of observational studies, including confounding bias and reverse causality. Mechanisms by which placental weight might influence health are yet to be fully explored. Recent findings suggest the placenta's role in metabolic programming and

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immune system development can affect future disease risk. For example, alterations in fetal growth pathways caused by placental dysfunction could elevate metabolic syndrome risk in later life [7]. Traditional cohort studies, while informative, face challenges in long-term assessments of these mediating pathways.

Recent genome-wide association studies (GWAS) have unveiled genetic determinants of placental weight, identifying 40 loci associated with its variability [8]. Mendelian randomization (MR) analysis offers a powerful method to infer causal relationships while minimizing the impact of confounding and reverse causality [9,10]. However, to date, no studies have reported the use of MR methods to explore the relationship between placental weight and adult disease risk.

This study employs GWAS data analyzing placental weight through a two-sample MR approach, focusing specifically on its causal relationship with type 2 diabetes (T2DM) and potential mediators including dietary habits and immune responses. The findings may facilitate understanding of early-life events and public health strategies for prevention and intervention.

2. Materials and methods

2.1. Exposure, outcome and mediator data

This study utilized GWAS summary data from reliable consortia predominantly involving individuals of European ancestry, except for two datasets including mixed populations. These datasets were considered to minimize potential population stratification bias (Fig. 1, Table S1). Data were extracted between July 1, 2024, and September 30, 2024.

For fetal placental weight (FPW), we analyzed summary-level data from a meta-analysis GWAS comprising 65,405 individuals of European ancestry, examining fetal genotype associations with placental weight, adjusted for sex and gestational age [8]. Additionally, we also performed analyses using the fetal GWAS of placental weight adjusted for fetal sex only as a replication dataset to validate our findings.

Four datasets were available for T2DM. We employed data from the DIAbetes Genetics Replication and Meta-analysis (DIAGRAM) consortium as the primary cohort, including 242,283 cases and 1,569,734 controls of European ancestry [11]. For replication, GCST006867 incorporated 61,714 European ancestry cases and 593,952 controls [12], while GCST90029024 comprised 468,298 European ancestry individuals and GCST90435704 included 18,945 British ancestry cases [13,14].

GWAS data for other common adult diseases were predominantly sourced from the FinnGen study (R11, Public release: June 24, 2024), with disease diagnoses conforming to the corresponding standards in ICD-9 or ICD-10. This large-scale initiative connects Finnish biobank samples with genetic data to study disease mechanisms [15].

We selected 35 blood and urine biomarkers (including metabolic and kidney function markers) to examine the causal effects of placental weight on T2DM-related biomarkers, drawn from a GWAS of 354,455 individuals, mainly of European ancestry (96.3 %) (GWAS Catalog ID: GCST90019492 to GCST90019526) [16].

We identified 43 environmental and lifestyle factors as potential mediators for the placental weight-T2DM pathway. These included 8 environmental exposures, 9 exercise and sleep characteristics, 13 dietary features, and 13 drug exposures, selected based on public health significance, modifiability, and availability of GWAS data from large cohorts with minimal overlap. Data were sourced from the UK Biobank study via the MRC IEU OpenGWAS platform (<https://gwas.mrcieu.ac.uk/>) [17,18].

Additionally, we also selected 731 immune cell phenotypes (B cells, classical dendritic cells, mature T cells, monocytes, regulatory T cells, myeloid cells, and TBNK cells) as potential mediators linking placental weight to T2DM. These phenotypes include 118 Absolute count, 192 Relative count, 32 Morphological parameters, and 389 Mean

Fluorescence Intensity measurements, all derived from European populations (GWAS Catalog ID: GCST90001391 to GCST90002121) [19].

2.2. Instrument variable selection

To ensure valid causal inference in MR analyses, instrumental variables (SNPs) must meet three key assumptions: relevance (significant association with exposure), independence (no association with confounders), and exclusion restriction (affecting outcomes solely through exposure). This study employed a rigorous SNP selection strategy, selecting SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$) in GWAS, with more stringent thresholds ($P < 5 \times 10^{-10}$, $P < 5 \times 10^{-28}$, or $P < 5 \times 10^{-58}$) for specific analyses. If no SNPs met these criteria, a relaxed threshold of $P < 5 \times 10^{-6}$ was applied. SNP selection was optimized through linkage disequilibrium (LD) pruning ($r^2 < 0.001$, distance window 10,000 kb) and allele harmonization. We documented the P-value selection strategy for transparency and reproducibility. To identify SNPs potentially linked to confounding factors, we conducted a comprehensive search in the GWAS Catalog (<https://www.ebi.ac.uk/gwas/>) [9,20], evaluating all reported phenotypes related to each SNP. This approach helped identify potential confounding relationships, enabling the exclusion of SNPs that might introduce bias.

2.3. Mediator screening

To assess the causal relationship between placental weight and T2DM, we conducted mediation analyses. Candidate mediators fell into two categories: (1) environmental and lifestyle factors, such as exposures, habits, dietary patterns, and medication use; and (2) biomarkers, including immune cell phenotypes. We screened potential mediators based on four criteria: (1) a causal relationship exists between placental weight and the mediator; (2) a causal relationship exists between the mediator and T2DM, not the reverse; (3) the mediator has a direct causal effect on T2DM independent of placental weight; and (4) the mediation direction aligns with the overall causal effect. Results with consistent effect directions, significant in both univariable MR (UVMR) and multivariable MR (MVMR) analyses ($p < 0.05$), and free from significant heterogeneity or horizontal pleiotropy were selected. Finally, we calculated the mediation effect and its proportion using the “product of coefficients” method ($\beta_1 \times \beta_2$) and performed sensitivity analyses to assess result robustness.

2.4. Statistical analysis

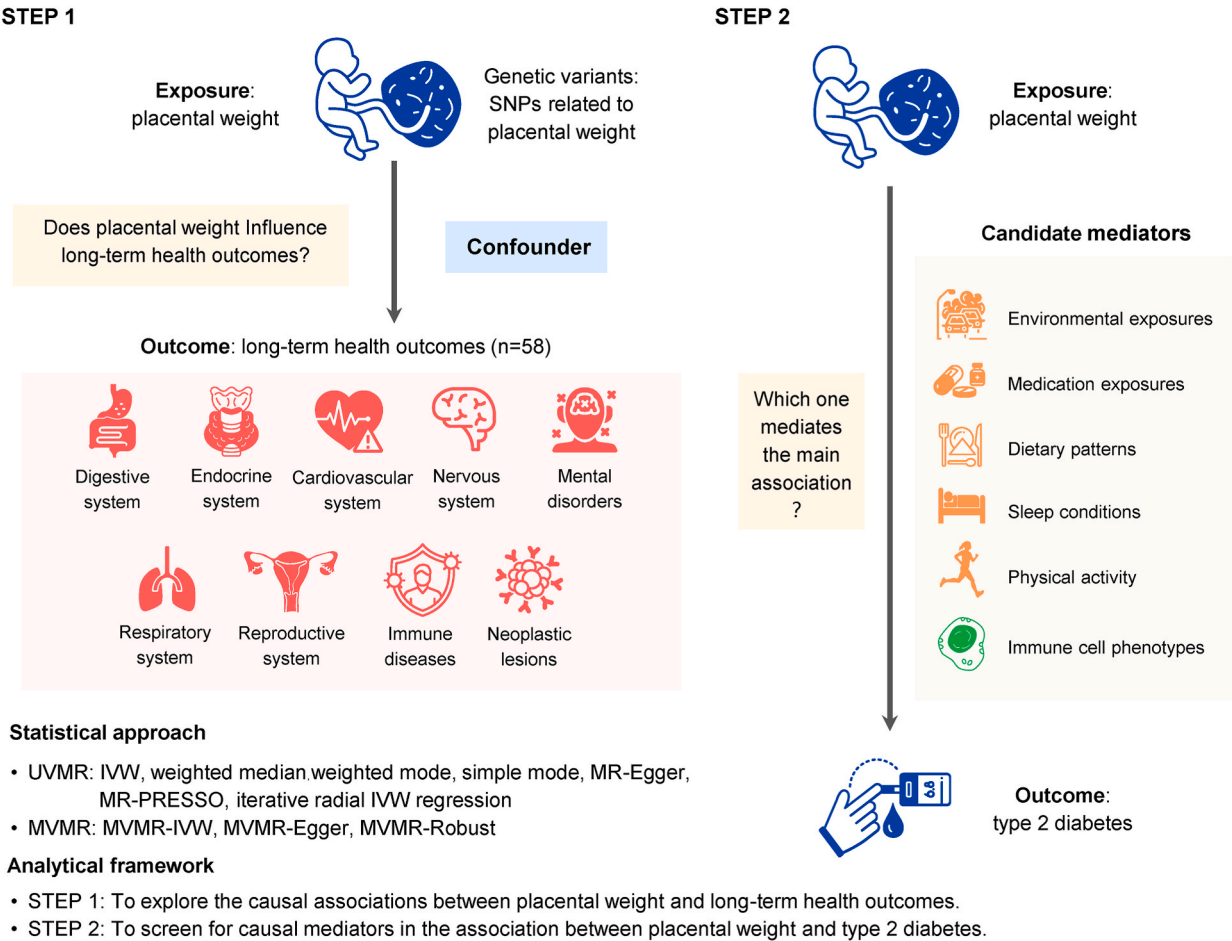
In UVMR analyses, we primarily utilized the inverse-variance weighted (IVW) method and validated results with weighted median, weighted mode, and simple mode methods (Table S2). To assess horizontal pleiotropy, we employed MR-Egger regression, while heterogeneity and outlier detection were conducted via the MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test and leave-one-out analysis.

We applied iterative radial IVW regression for causal assessment and robustness verification, using modified second-order weights for IVW and MR-Egger regressions. A Bonferroni-corrected significance level of $\alpha = 0.05/\text{nrow}(\text{dat})$ was used for Cochran's Q statistic to test heterogeneity. In MVMR analyses, the MVMR-IVW method was used, with robustness checked using the MVMR-Robust method. MVMR-Egger regression detected horizontal pleiotropy. We assessed instrument variable validity through conditional F-statistics and evaluated horizontal pleiotropy with a modified Cochran's Q statistic to distinguish pleiotropy from weak instruments.

Causal associations were deemed valid only if IVW estimates were directionally consistent and significant in at least one sensitivity analysis. This comprehensive application of methods facilitated robust causal inferences and minimized biases.

To evaluate mediating roles of environmental and lifestyle factors, as well as biomarkers, in the relationship between placental weight and

A



B

Phenotype	Identifier	Sample size (case / control)	Ancestry	Consortium or GWAS ID	Year of publication or release	PMID
Fetal placental weight	FPW	65,405	European	EGG	2023	37798380
Childhood body mass index	Childhood BMI	39,620	European	EGG	2020	33045005
Birth weight	BW	298,142	European	EGG	2019	31043758
Type 2 diabetes	DIAGRAM T2DM	242,283 / 1,569,734	European	DIAGRAM	2024	38374256
Type 2 diabetes	GC67 T2DM	61,714 European cases + 1,178 Pakistani cases / 593,952 European controls + 2,472 Pakistani controls		GCST006867	2018	30054458
Type 2 diabetes	GC24 T2DM	468,298	European	GCST90029024	2018	29892013
Type 2 diabetes	GC04 T2DM	18,945 / 388,756	European	GCST90435704	2018	30104761
Type 1 diabetes	GC29 T1DM	7,467 / 10,218	European	GCST90000529	2021	33830302
Type 1 diabetes	GC64 T1DM	2,751 / 324,074	European	GCST90014464	2021	34278373
Type 1 diabetes	GC35 T1DM	367 / 455,981	European	GCST90043635	2021	34737426
Immune cell traits	ICs	3,757	European	GCST90001391 to GCST90002121	2020	32929287

Fig. 1. Study design and data characteristics for Mendelian randomization (MR) analysis. (A) Schematic representation of the two-step MR approach. STEP 1: MR analysis to investigate causal relationships between placental weight and long-term health outcomes. Genetic variants associated with placental weight are used as instrumental variables to assess their effects on various health outcomes. STEP 2: Mediation analysis to identify potential causal mediators in the association between placental weight and type 2 diabetes, elucidating potential biological pathways. (B) Main characteristics of genome-wide association study (GWAS) datasets utilized in the study. This panel summarizes key information about the GWAS data sources, including sample sizes, ancestry, consortium or GWAS ID and PMID. Detailed information on all GWAS datasets used in this study is provided in [Table S1](#).

T2DM, we conducted UVMR analyses, assessing: (1) the causal effect of placental weight on each potential mediator; (2) each mediator's causal effect on T2DM; and (3) reverse MR analyses to identify bidirectional relationships. Based on UVMR findings, MVMR analyses included placental weight and mediators as exposures, with T2DM as the outcome, testing whether the mediator affects T2DM independently of placental weight.

The mediation proportion was calculated as the product of the effects of placental weight on the mediator (β_1) and the mediator on T2DM (β_2), divided by the total effect of placental weight on T2DM (β). The 95 % CI for mediation proportions were derived using the delta method, truncating negative values to 0 %. Sensitivity analyses were applied for reliability.

MR results are reported as odds ratios (ORs), β coefficients, or proportions with respective 95 % CIs. All MR analyses were conducted using R software (version 4.3.2). The R packages employed in the analyses include TwoSampleMR (version 0.6.8), MVMR (version 0.4), MendelianRandomization (version 0.10.0), MRPRESSO (version 1.0), RadialMR (version 1.1), and dplyr (version 1.1.4). P-values < 0.05 were considered statistically significant. Figures and charts were created using GraphPad Prism (version 9.5.0, GraphPad Software, LLC), while the study design overview was illustrated using Canva (www.canva.com).

This study adhered to the recommendations of the MR guideline and the Strengthening the Reporting of Observational Studies in Epidemiology (Supplementary STROBE-MR checklist) [21,22].

3. Result

3.1. Overall effects of placental weight on long-term health outcomes

An overview of the study design is presented in Fig. 1. We initially performed MR analysis using the iterative radial IVW regression method to evaluate the potential causal effects of placental weight on various long-term health outcomes. For diabetes and endocrine diseases, the analysis indicated a significant association, where a one standard deviation increase in placental weight was linked to approximately a 0.85 % reduction in risk ($\beta = -0.009$, 95 % CI: -0.017 to 0.000 , $P = 0.044$). Similarly, acute upper respiratory infections showed a significant inverse association ($\beta = -0.062$, 95 % CI: -0.113 to -0.011 , $P = 0.017$). Conversely, higher placental weight was associated with a 13.0 % increased risk of basal cell carcinoma ($\beta = 0.130$, 95 % CI: 0.016 to 0.245 , $P = 0.026$). Significant inverse associations were also observed for neurological diseases ($\beta = -0.009$, 95 % CI: -0.014 to -0.003 , $P = 0.002$) and malignant neoplasm of the endometrium ($\beta = -0.561$, 95 %

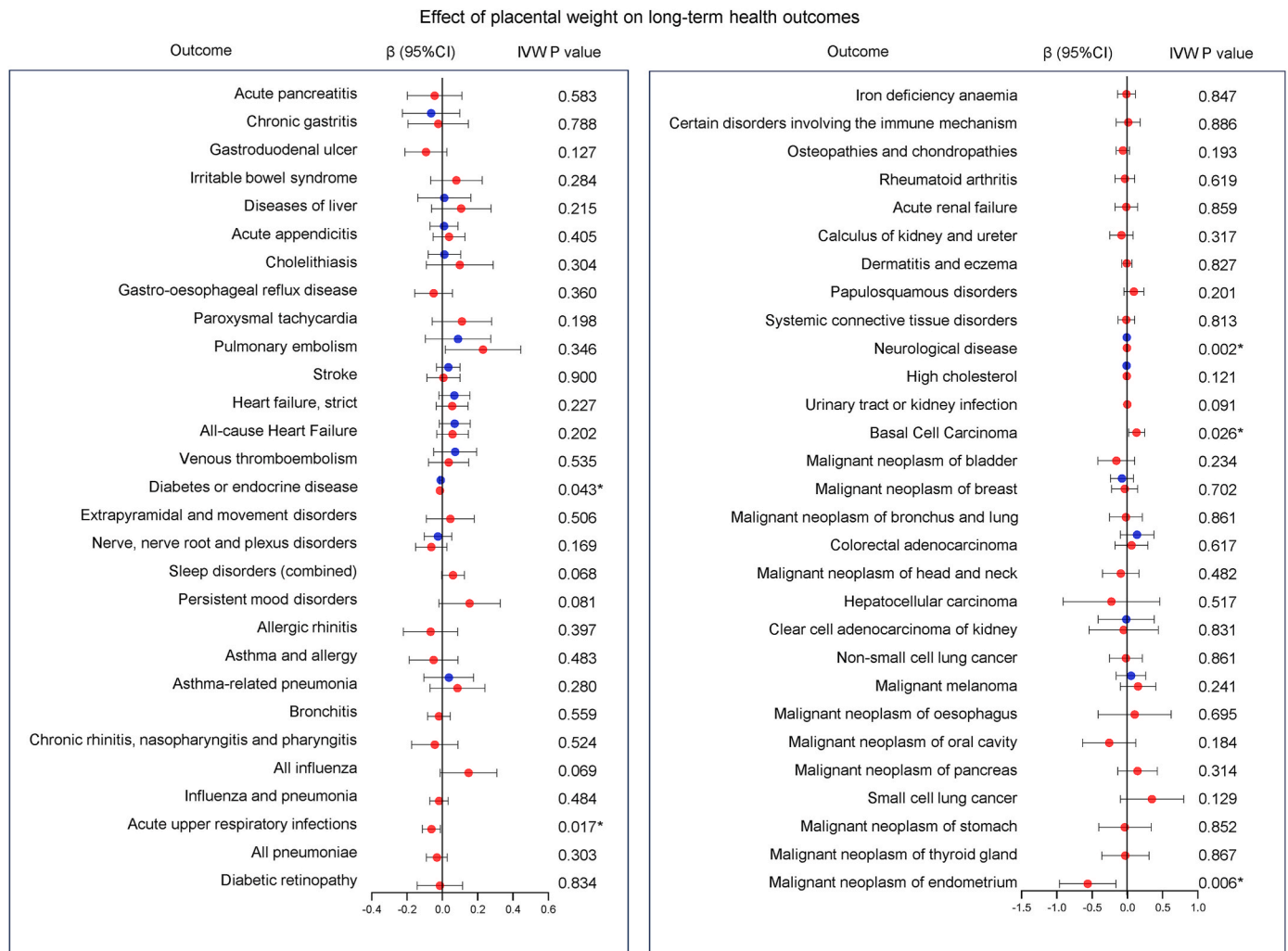


Fig. 2. MR analysis of the causal effects of placental weight on long-term health outcomes. The MR estimates were derived using the iterative radial inverse-variance weighted (IVW) regression method, assessing the potential causal effects of placental weight on multiple long-term health outcomes. For each outcome, the plot displays β coefficients with 95 % confidence intervals (95 % CI) and associated P-values. Red dots represent the initial radial IVW estimates (radial 1), and blue dots indicate the second iteration of radial IVW estimates (radial 2). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

CI: -0.961 to -0.161 , $P = 0.006$) (Tables S3 and S4). No significant causal relationships were found for other health outcomes (all $P > 0.05$) (Fig. 2, Table S3).

To enhance the robustness of MR estimates, we applied iterative radial regression to identify outliers. For diabetes and endocrine diseases, Cochran's Q statistic indicated no substantial heterogeneity ($Q = 28.15$, $df = 21$, $P = 0.136$), and no significant horizontal pleiotropy was detected via the MR-Egger regression intercept (intercept = -0.830 , $SE = 1.602$, $P = 0.610$) or MR-PRESSO global test ($P = 0.143$). Similar results were observed for basal cell carcinoma ($Q = 36.69$, $df = 28$, $P = 0.126$), neurological diseases ($Q = 21.52$, $df = 21$, $P = 0.427$), and malignant neoplasm of the endometrium ($Q = 18.54$, $df = 21$, $P = 0.615$), with no significant horizontal pleiotropy indicated in any case (Tables S3 and S4).

3.2. Causal effect of placental weight on type 2 diabetes

Given the potential causal effect of placental weight on diabetes or endocrine diseases, then we focused on validating the causal relationship between placental weight and diabetes (Fig. 3A). In the primary cohort (DIAGRAM T2DM, $n = 1,812,017$), IVW analysis revealed a significant negative correlation between placental weight and T2DM ($\beta = -0.109$, 95 % CI: -0.184 to -0.034 , $P = 0.004$), suggesting a one standard deviation increase in placental weight is associated with approximately a 10.3 % reduction in T2DM (OR = 0.897, 95 % CI: 0.832 to 0.966) (Fig. 3B, Table S5). Other MR methods, including MR-Egger and Weighted median, showed similar trends, with the latter reaching statistical significance (Fig. 3B, Fig. S1 and Table S5). Iterative radial regression provided robust estimates, resulting in $\beta = -0.122$ (95 % CI: -0.183 to -0.061 , $P < 0.0001$) after four iterations using 18 SNPs, and this remained significant post-outlier removal. Leave-one-out analysis indicated no single SNP significantly influenced the causal estimate (Fig. S2).

In three T2DM replication cohorts, consistent negative correlations were observed: GC24 T2DM ($\beta = -0.007$, $P = 0.002$), GC04 T2DM ($\beta = -0.153$, $P = 0.021$), and GC67 T2DM ($\beta = -0.069$, $P = 0.249$), with the first two achieving statistical significance (Fig. 3B, Table S5). Iterative radial regression analysis confirmed significance for all cohorts: GC24 T2DM ($\beta = -0.007$, $P = 0.002$), GC04 T2DM ($\beta = -0.153$, $P = 0.021$), and GC67 T2DM ($\beta = -0.117$, $P = 0.039$) (Fig. 3B, Table S6). Furthermore, a significant negative correlation was noted between placental weight and insulin fold change during oral glucose tolerance tests ($\beta = -0.115$, $P = 0.012$) (Fig. 3C, Table S7).

MR-Egger regression did not detect significant horizontal pleiotropy (all $P > 0.05$), validating the instrumental variables. The MR-PRESSO global test identified outliers in some analyses, but the main findings remained consistent post-removal (Tables S5–S7). Finally, reverse MR indicated no significant association between T2DM and placental weight (Table S8).

Furthermore, no significant causal relationship between placental weight and T1DM was found, with IVW analysis showing non-significant results across three T1DM cohorts (Fig. 3B, Tables S5 and S6). Additional MR methods reinforced the absence of significant associations in T1DM.

3.3. Multivariable MR analysis of the causal relationship between placental weight and T2DM

To further validate the relationship between placental weight and T2DM while considering potential confounding factors, we conducted MVMR analysis. After adjusting for childhood BMI, placental weight maintained a significant negative correlation with T2DM risk ($\beta = -0.30$, 95 % CI: -0.54 to -0.06 , $P = 0.020$). Concurrently, childhood BMI showed a positive correlation with T2DM ($\beta = 0.52$, 95 % CI: 0.33 to 0.71, $P = 4.82 \times 10^{-6}$) (Fig. 3D, Table S9). These results were consistent in MVMR-Egger and MVMR-Robust analyses, supporting their

robustness. F-statistics greater than 10 indicated strong instrumental variables, with no significant bias found in directional pleiotropy tests (Table S9).

In another MVMR model considering both placental and birth weight, the negative correlation between placental weight and T2DM became more significant after adjusting for birth weight ($\beta = -0.56$, 95 % CI: -0.84 to -0.28 , $P = 1.65 \times 10^{-4}$), while birth weight showed no significant association with T2DM ($\beta = 0.05$, $P = 0.720$) (Fig. 3D, Table S9). Although lower F-statistics in this model (placental weight: 5.10; birth weight: 4.20) suggest caution, MVMR-Egger and MVMR-Robust analyses aligned with main findings, and the Egger intercept test ($P = 0.214$) confirmed no significant directional pleiotropy, enhancing credibility (Table S9).

3.4. Causal effect of placental weight on T2DM-related blood and urine biomarkers

We also investigated the causal effects of placental weight on 35 blood and urine biomarkers that are related to T2DM pathophysiology. We identified significant associations between placental weight and several key biomarkers. Notably, placental weight showed significant negative correlations with blood glucose levels ($\beta = -0.102$, 95 % CI: -0.200 to -0.004 , $P = 0.041$). We observed significant negative associations with both creatinine levels ($\beta = -0.058$, 95 % CI: -0.090 to -0.026 , $P = 0.0003$) and serum phosphate levels ($\beta = -0.034$, 95 % CI: -0.065 to -0.002 , $P = 0.037$), while a positive association was found with estimated glomerular filtration rate ($\beta = 0.056$, 95 % CI: 0.026 to 0.086, $P = 0.0002$) (Table S10). The robustness of these findings was confirmed through multiple sensitivity analyses.

3.5. Mediating role of environmental and lifestyle factors in the relationship between placental weight and T2DM

We analyzed the mediating effects of environmental and lifestyle factors in the relationship between placental weight and T2DM using a two-step MR mediation analysis. Placental weight was significantly associated with four potential mediators: metformin use ($\beta = -0.006$, $P = 0.003$), water intake ($\beta = 0.034$, $P = 0.011$), dried fruit intake ($\beta = 0.022$, $P = 0.012$), and pork intake ($\beta = -0.016$, $P = 0.023$), with robust associations confirmed by iterative radial regression (Fig. 4A, Table S11). Metformin use correlated positively with T2DM risk ($\beta = 25.42$, $P = 2.29 \times 10^{-53}$), and dried fruit intake showed a significant negative correlation ($\beta = -1.15$, $P = 3.24 \times 10^{-18}$). However, pork intake did not reach statistical significance ($P > 0.05$) (Fig. 4B, Table S12). Sensitivity analyses confirmed the reliability of the associations for metformin and dried fruit intake, while water intake showed a weak yet significant correlation.

Further analysis of dried fruit intake revealed a significant negative association with T2DM independent of placental weight ($\beta = -0.809$, $P = 0.001$), whereas placental weight also showed a negative correlation ($\beta = -0.246$, $P = 0.004$). Directional pleiotropy tests indicated no significant direct effect (Egger intercept = 0.004, $P = 0.289$), and mediation analysis suggested dried fruit intake accounts for 14.68 % of the pathway linking placental weight to T2DM (Fig. 4C and D, Tables S13 and S14).

3.6. Mediating role of immune cell phenotypes

To explore biological mechanisms underlying the causal relationship, we analyzed 731 immune cell phenotypes. We identified 51 phenotypes as potential mediators, including various B cell and T cell subtypes (Fig. 5A, Tables S15 and S16). Among these, six immune cell phenotypes showed potential associations with T2DM (Fig. 5B, Table S17). Notably, CD24 expression on memory B cells positively correlated with T2DM ($\beta = 0.014$, $P = 0.0016$), while HLA DR on CD33dim HLA DR + CD11b + exhibited a significant negative

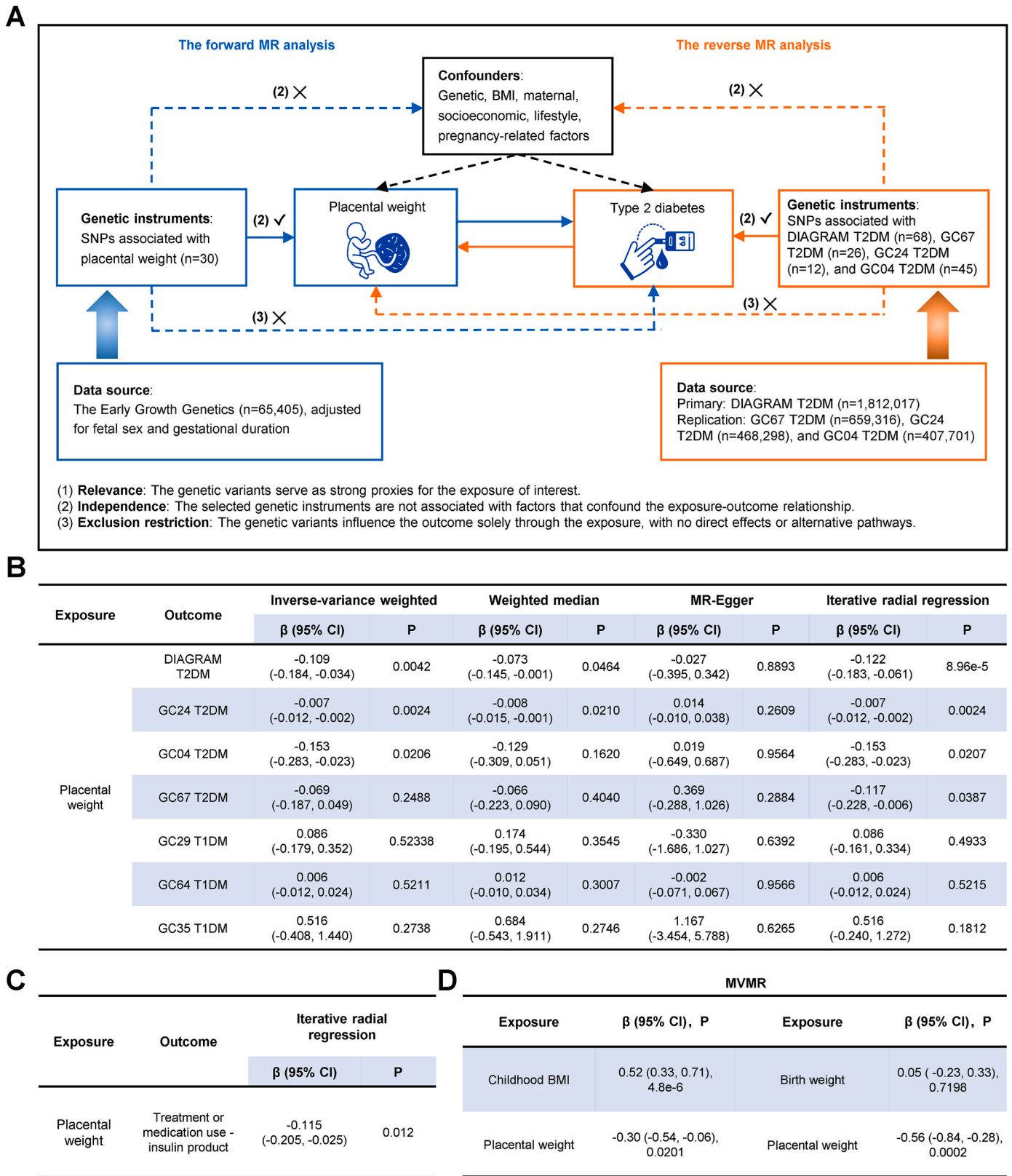


Fig. 3. Causal relationship between placental weight and type 2 diabetes. (A) Schematic overview of the MR study design, illustrating the hypothesized causal relationship between placental weight and type 2 diabetes. (B) Univariate MR (UVMR) estimates of the effect of placental weight on diabetes, presenting results from multiple MR methods including IVW, weighted median, MR-Egger, and iterative radial IVW regression. (C) UVMR estimates of placental weight’s impact on insulin-related trait, presenting result from IVW. (D) Results of multivariable MR (MVMR) analyses adjusted for potential confounding factors (childhood BMI and birth weight).

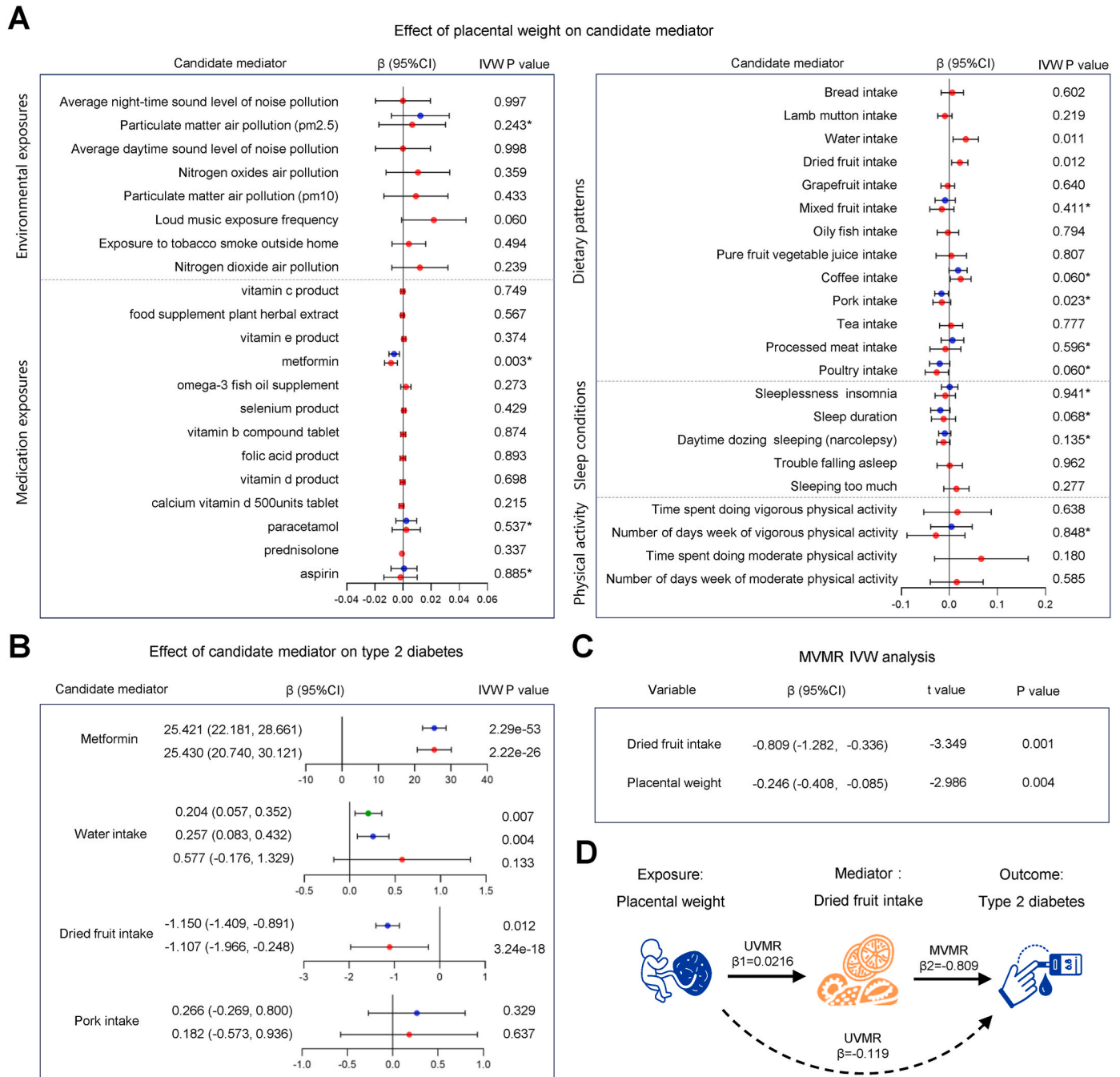


Fig. 4. Mediation MR analysis of environmental and lifestyle factors in the causal relationship between placental weight and type 2 diabetes. (A) Forest plot illustrating the effect of placental weight on candidate mediators. (B) Forest plot depicting the effect of candidate mediators on T2DM. For each outcome, the plot displays β coefficients with 95 % confidence intervals (95 % CI) and associated P-values. Red dots represent initial radial IVW estimates (radial 1), blue dots show estimates after one iteration (radial 2), and green dots display estimates after two iterations (radial 3). (C) MVMR analyses results showing the effect of candidate mediators (Dried fruit intake) on T2DM after adjusting for the influence of placental weight. (D) Schematic diagram illustrating the mediation pathway from placental weight to T2DM through the candidate mediator (Dried fruit intake), displaying β , β_1 , and β_2 coefficients. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

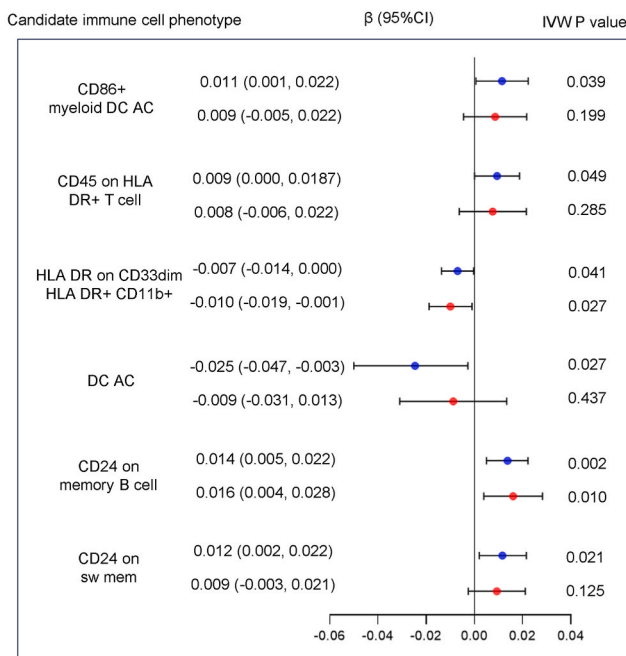
correlation ($\beta = 0.007$, $P = 0.0408$). MVMR analysis showed that HLA DR on CD33dim HLA DR + CD11b + remained negatively correlated with T2DM after adjusting for placental weight ($\beta = -0.270$, $P = 0.026$), while placental weight's direct effect was non-significant ($\beta = -0.018$, $P = 0.705$) (Fig. 5C, Tables S18 and S19). Mediation analysis suggested HLA DR on CD33dim HLA DR + CD11b + may fully mediate the relationship with a mediation proportion of 131 %. However, the weak strength of instrumental variables for placental weight ($F = 6.02$) and significant heterogeneity ($Q = 233.92$, $P < 1.38 \times 10^{-42}$) necessitate

cautious interpretation and further validation (Table S19).

4. Discussion

This study employs MR to explore causal relationships between placental weight and long-term health outcomes, particularly T2DM, using the latest large-scale GWAS data. Our findings shed light on how placenta impacts health in early life and inform prevention and intervention strategies.

■ Qualified in a certain process ■ Potential mediator

[illegible]

Variable	β (95%CI)	t value	P value
HLA DR on CD33dim HLA DR+ CD11b+	-0.270 (-0.482, -0.058)	-2.494	0.025
Placental weight	-0.018 (-0.108, 0.072)	-0.387	0.705
CD86+ myeloid DC AC	0.004 (-0.050, 0.057)	0.145	0.886
Placental weight	-0.272 (-0.434, -0.111)	-3.304	0.003
CD45 on HLA DR+ T cell	0.072 (-0.023, 0.167)	1.483	0.151
Placental weight	-0.250 (-0.409, -0.092)	-3.091	0.005

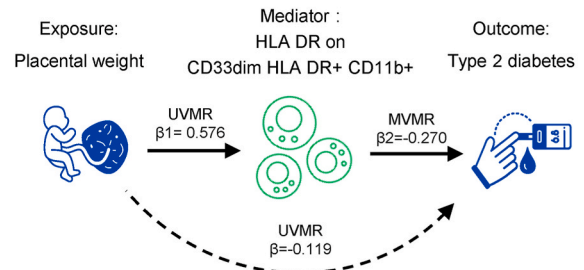


Fig. 5. Mediation MR analysis of immune cell phenotypes in the causal relationship between placental weight and type 2 diabetes. (A) Four-step screening process was employed to identify potential immune cell mediators. Step 1: The immune cell phenotype should be causally associated with placental weight. Step 2: Type 2 diabetes should be causally associated with the immune cell phenotype, but not vice versa. Step 3: The immune cell phenotype should have a direct causal effect on type 2 diabetes independent of placental weight. Step 4: The direction of the mediation path should align with the total causal effect. (B) Forest plot depicting the effect of candidate mediators on T2DM. For each outcome, the plot displays β coefficients with 95 % confidence intervals (95 % CI) and associated P-values. Red dots represent initial radial IVW estimates (radial 1), and blue dots show estimates after one iteration (radial 2). (C) MVMR analyses results showing the effect of candidate mediators on T2DM after adjusting for the influence of placental weight. (D) Schematic diagram illustrating the mediation pathway from placental weight to T2DM through the candidate mediator (HLA DR on CD33dim HLA DR + CD11b +), displaying β , β_1 , and β_2 coefficients. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Evidence indicates that fetal-placental vascular dysfunction is a prenatal determinant of adult cardiovascular disease. Low birth weight correlates with higher risks of coronary heart disease, stroke, hypertension, and type 2 diabetes, potentially stemming from “programming” during critical fetal stages as the fetus adapts to inadequate placental nutrient supply [23]. Additionally, fetal overgrowth is linked to methylation changes in the placental genome, which relate to future metabolic health [24]. Our MR analysis reveals causal links between placental weight and several health outcomes, emphasizing the placenta’s role as an interface between maternal conditions and fetal development. The study supports the DOHaD hypothesis, highlighting how early life, particularly placental development, can influence long-term health.

A significant finding is the negative correlation between placental weight and T2DM, validated across multiple GWAS cohorts with over 1.8 million individuals. Each standard deviation increase in genetically predicted placental weight correlates with a 10.3 % reduction in T2DM odds. This aligns with findings by Sánchez-Soriano et al., [25] who found lower placental weight in offspring linked to increased T2DM risk in fathers. Our analyses also show negative associations between placental weight and blood glucose, creatinine, and serum phosphate levels, supporting the relationship with T2DM risk, particularly since elevated creatinine indicates diabetic nephropathy progression and serum phosphate is linked to diabetic retinopathy (DR) [26–28]. Furthermore, our findings of significant inverse associations between placental weight and neurological diseases are consistent with previous clinical observations. For instance, studies have shown that low placental weight is significantly associated with increased risk of cerebral palsy, particularly bilateral spastic cerebral palsy in term infants [29], supporting the broader implications of placental weight in neurological outcomes.

Previous research has explored interactions between the placenta and diabetes, such as increased capillary volumes in placentas from poorly controlled diabetes and the association of early placental IGFBP1 levels with insulin resistance [30,31]. Moreover, unique gene expression characteristics in the placenta correlate with gestational diabetes and T2DM [32]. Factors like placental macrophage-derived IL-32 and insulin/IGF-1 signaling pathways highlight the connection between placental function and metabolic outcomes [33,34]. Our study establishes a genetic association between placental weight and adult-onset diabetes, contributing valuable insights into this critical area of research.

Our findings suggest that lifestyle factors mediate the association between placental weight and T2DM. Placental weight is significantly linked to various environmental factors, including metformin use, water intake, dried fruit intake, and pork consumption, implying that the placenta may influence long-term health through metabolic and dietary behaviors [35–37]. Notably, dried fruit intake shows a significant negative correlation with T2DM, consistent with literature indicating that increased consumption may mitigate T2DM risk [38,39]. Mediation analysis reveals that dried fruit intake accounts for 14.68 % of the effects of placental weight on T2DM, underscoring the interactions between early life factors and later lifestyle choices, and highlighting the importance of a life course approach in chronic disease pathogenesis.

Inflammation is central to diabetes development, with immune cell-mediated attacks crucial for impaired insulin secretion and insulin resistance in T2DM [40]. Single-cell RNA sequencing (scRNA-seq) of peripheral blood mononuclear cells (PBMCs) from non-diabetic and T2DM patients revealed that CD14 monocytes in T2DM are pro-inflammatory, while intermediate monocytes express more MHC class II genes. Cytotoxic CD4 T cells, effector memory CD8 T cells, and $\gamma\delta$ T cells showed increased cytotoxicity and clonal expansion [41]. Immune infiltration analysis indicated higher eosinophils, CD4 naive T cells, and regulatory T cells (Tregs) in T2DM, while CD4 memory resting T cells and monocytes were lower [42]. Macrophages primarily drive inflammation in islets and insulin target organs, affecting β cell insulin

secretion through polarization and cytokine production [43]. Recent MR studies found a causal link between increased monocyte counts and T2DM risk, with CD8⁺ T cell and CD4⁺ CD8dim T cell counts influencing susceptibility [44]. Another study showed that among four immune characteristics (MFI, RC, AC, and MP), 35 immune cell phenotypes were associated with the risk of DR, while DR led to expression changes in 26 immune cells [45]. Wu et al. [46] demonstrated that cationic nanoparticles disguised as macrophages could reduce pro-inflammatory cytokine production and insulin resistance, suggesting potential for immune cell-based therapies in T2DM.

Our MR analysis indicated that the HLA DR on CD33dim HLA DR + CD11b + phenotype mediates the influence of placental weight on T2DM. This immune cell phenotype may serve as an independent protective factor, with mediation analysis suggesting it fully mediates the relationship between placental weight and T2DM, showing a mediation proportion of 131 %. While this finding indicates complete mediation, the proportion exceeding 100 % likely reflects the presence of suppression effects or intricate biological pathways not fully captured in our current model. Several factors may contribute to this observation, including the relatively modest instrumental variable strength for placental weight and potential unmeasured confounding pathways. This pattern is not uncommon in complex biological systems where multiple interconnected pathways may exist. These results underscore both the robust involvement of immune-mediated mechanisms in the placental weight-T2DM relationship and the need for additional mechanistic studies to fully elucidate these biological interactions.

Our study has several strengths. First, it utilizes large-scale GWAS data from multiple independent cohorts, providing robust statistical power for causal inference and supporting the reliability of our conclusions. Second, we employed various MR methods and sensitivity analyses to ensure the robustness of our findings. Third, our UVMR and MVMR analyses adjusted for potential confounders, such as childhood BMI and birth weight, yielding precise estimates of causal relationships. Fourth, we identified the causal link between placental weight and T2DM while exploring biological mechanisms through T2DM-related biomarkers, offering insights into underlying pathways. Finally, our identification of dried fruit intake as a significant mediator presents practical implications for intervention strategies.

However, this study has several limitations. Although MR provides strong causal evidence, it relies on assumptions regarding the validity of instrumental variables that are not always verifiable. While our findings primarily derive from European populations, highlighting a need for caution in generalizing these results, they provide crucial foundational evidence for the role of placental weight in later-life health outcomes. Subsequent studies incorporating diverse populations and considering population-specific genetic and environmental factors will be essential to validate and extend these findings across different ancestral groups. Additionally, future research should delve into the biological mechanisms connecting placental weight to long-term health, particularly focusing on T2DM-related molecular pathways in placental tissue. Public health validation in multi-ethnic populations is crucial, alongside prospective cohort studies that combine placental weight measurements with long-term follow-up. Finally, intervention studies should assess the potential of improving placental function or implementing early lifestyle changes to reduce long-term health risks. Moreover, while we also acknowledge the current limitation that placental weight can only be measured postpartum, our findings extend beyond just using placental weight as a predictive marker. The identified causal pathways and mediating mechanisms provide valuable insights for developing preventive strategies during pregnancy through modifiable factors that influence placental development, as well as informing post-delivery risk assessment and targeted interventions for metabolic health.

5. Conclusion

In conclusion, our study establishes causal relationships between

placental weight and long-term health outcomes, especially its association with T2DM, while highlighting immune-mediated pathways. These findings enhance our understanding of early life factors influencing long-term health and offer new insights for prevention strategies. Emphasizing prenatal care and early interventions may significantly improve population health outcomes. Future research should focus on elucidating specific biological mechanisms and translating these findings into effective public health strategies.

CRedit authorship contribution statement

Qinyi Zhang: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Tianhan Xu:** Methodology, Investigation, Formal analysis. **Sihui Yu:** Formal analysis, Data curation. **Sufang Wu:** Writing – review & editing, Conceptualization. **Ye Yang:** Writing – review & editing, Methodology, Data curation. **Hao Wu:** Writing – review & editing, Resources. **Jiawen Zhang:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Ethics approval and consent to participate

All summary-level GWAS data utilized in our analyses are publicly available, thereby exempting this study from ethical review. The ethical approvals for the original GWAS can be found in the corresponding GWAS publications cited in this manuscript.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.placenta.2025.03.006>.

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序号	标题	作者	排名	出处	JCR分区	影响因子	文献类型	被引频次	入藏号
1	CHMP4B and VSP4A reverse GSDMD-mediated pyroptosis by cell membrane remodeling in endometrial carcinoma	Yang, Y; Chen, HL; Wu, SF; Bao, W	第一作者	JAN 2024 NOV 2023(在线发表) BIOCHIMICA ET BIOPHYSICA ACTA-GENERAL SUBJECTS 1868(1)	BIOCHEMISTRY & MOLECULAR BIOLOGY Q3;BIOPHYSICS (SCIE) (2023年)	2.8 (2023年)	Article	1	WOS:0011 170689000 01
2	Molecular subtypes of endometrial cancer: Implications for adjuvant treatment strategies	Yang, Y; Wu, SF; Bao, W	第一作者	FEB 2024 JUL 2023(在线发表) INTERNATIONAL JOURNAL OF GYNECOLOGY & OBSTETRICS 164(2), pp.436-459	OBSTETRICS & GYNECOLOGY (SCIE) (2023年)	2.6 (2023年)	Review	11	WOS:0010 379202000 01
3	Effect of hypoxia-HIF-1 α -periostin axis in thyroid cancer	Yang, Y; Wu, JY(...);Wang, M	共同一作, 排名第一	APR 2024 ONCOLOGY REPORTS 51(4)	ONCOLOGY Q2 (SCIE) (2023年)	3.8 (2023年)	Article	0	WOS:0012 152744000 01
4	Retrospective analysis of the 18F-FDG PET/CT cutoff value for metabolic parameters was performed as a prediction model to evaluate risk factors for endometrial cancer	Yang, Y; Pan, YQ(...);Bao, W	第一作者	DEC 4 2023 RADIATION ONCOLOGY 18(1)	RADIOLOGY, NUCLEAR MEDICINE & MEDICAL IMAGING Q1;ONCOLOGY Q2 (SCIE)	3.3	Article	0	WOS:0011 136469000 01



序号	标题	作者	排名	出处	JCR分区	影响因子	文献类型	被引频次	入藏号
5	Technical, ergonomic and cognitive learning methodology in transumbilical single-port laparoscopic hysterectomy	Yang, Y; Gu, S(...); Wu, SF	第一作者	OCT 2023 MAY 2023(在线发表) INTERNATIONAL JOURNAL OF GYNECOLOGY & OBSTETRICS 163(1), pp.158-166	OBSTETRICS & GYNECOLOGY (SCIE) Q2	2.6	Article	0	WOS:000997468400001
6	Ergonomic learning curves on gynecological laparoendoscopic single-site (LESS) surgery	Yang, Y; Pan, YQ(...); Wu, SF	第一作者	OCT 27 2023 BMC SURGERY 23(1)	SURGERY Q2 (SCIE)	1.6	Article	1	WOS:001094236500005
7	The role of Vps4 in cancer development	Huang, LJ; Zhan, ST(...); Yang, Y	共同通讯, 排名最后	JUN 19 2023 FRONTIERS IN ONCOLOGY 13	ONCOLOGY Q2 (SCIE)	3.5	Review	1	WOS:001017942100001
8	Clinical and Pathological Characteristics of Patients With Papillary Thyroid Carcinoma Coexisting With Hashimoto's Thyroiditis: A Retrospective Cohort Study	Yang, Y; Liu, J; Shi, XQ; Wang, M	共同一作, 排名第一	AUG 2023 CANCER CONTROL 30	ONCOLOGY Q3 (SCIE)	2.5	Article	0	WOS:001058062700001
9	Student-Driven Course-Based Undergraduate Research Experience (CUREs) Projects in Identifying Vaginal Microorganism Species Communities to Promote Scientific Literacy Skills	Yang, Y; Wang, M(...); Wu, SF	共同一作, 排名第一	APR 28 2022 FRONTIERS IN PUBLIC HEALTH 10	PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH Q1(SCIE); PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH Q1(SSCI)	5.2	Article	2	WOS:000795914400001





序号	标题	作者	排名	出处	JCR分区	影响因子	文献类型	被引频次	入藏号
10	The endosomal sorting complex required for transport repairs the membrane to delay cell death	Yang, Y; Wang, M(...);Gu, S	第一作者	OCT 18 2022 FRONTIERS IN ONCOLOGY 12	ONCOLOGY Q2(SCIE)	4.7	Review	15	WOS:000878360200001
11	Genomic analysis of the endosomal sorting required for transport complex III pathway genes as therapeutic and prognostic biomarkers for endometrial carcinoma	Yang, Y; Wang, M	第一作者	SEP 2022 JUL 2022(在线发表) TRANSLATIONAL CANCER RESEARCH 11(9), pp.3108-+	ONCOLOGY Q4(SCIE)	0.9	Article	6	WOS:000839239400001
12	KRAS, YWHAE, SP1 and MSRA as biomarkers in endometrial cancer	Yang, Y; Sang, ZY(...);Wu, SF	第一作者	MAR 2021 TRANSLATIONAL CANCER RESEARCH 10(3), pp.1295-+	ONCOLOGY Q4(SCIE)	0.496	Article	6	WOS:000635021300011
13	Hydrogen inhibits endometrial cancer growth via a ROS/NLRP3/caspase-1/GSDMD-mediated pyroptotic pathway	Yang, Y; Liu, PY(...);Zhu, PY	共同一作, 排名第一	JAN 10 2020 BMC CANCER 20(1)	ONCOLOGY Q2(SCIE)	4.43	Article	116	WOS:000513702000002
14	RNA sequencing analysis reveals apoptosis induction by hydrogen treatment in endometrial cancer via TNF and NF-κB pathways	Yang, Y; Liu, YP(...);Xi, XW	第一作者	MAY 2020 TRANSLATIONAL CANCER RESEARCH 9(5), pp.3468-3482	ONCOLOGY Q4(SCIE)	1.241	Article	3	WOS:000538020100032



序号	标题	作者	排名	出处	JCR分区	影响因子	文献类型	被引频次	入藏号
15	γ -Glutamyl cyclotransferase contributes to endometrial carcinoma malignant progression and upregulation of PD-L1 expression during activation of epithelial-mesenchymal transition	Xu, SJ; Yang, Y(...); Li, YL	共同一作, 共2位共一	APR 2020 INTERNATIONAL IMMUNOPHARMACOLOGY 81	PHARMACOLOGY & PHARMACY Q2; IMMUNOLOGY Q2(SCIE)	4.932	Article	2	WOS:000527892200039
16	An Observation of a Resident-as-Teacher Combined with Tutor Guided Hysteroscopy Teaching Program for Standardized Residency Training (SRT) in Obstetrics and Gynecology	Yang, Y; Li, LY(...); Wu, FS	第一作者	JUL 30 2020 JOURNAL OF HEALTHCARE ENGINEERING 2020	HEALTH CARE SCIENCES & SERVICES Q2(SCIE)	2.682	Article	3	WOS:000561306100001

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