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ORIGINAL RESEARCH

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Causal inferences on childhood obesity and dentofacial anomalies: a mendelian randomization study

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Abstract

Background: Dentofacial anomalies, including malocclusion, can lead to functional impairment and psychosocial challenges. While genetics and environmental factors during growth and development play crucial roles, the impact of childhood obesity remains unclear. This study aimed to investigate the causal relationship between high body weight in childhood and dentofacial anomalies using Mendelian randomization (MR). **Methods**: A two-sample MR approach was applied using genome-wide association study data, which is a technique used in genetic epidemiology to infer causal relationships between exposures and outcomes using summary data from separate genetic association studies for each. This method leverages the random allocation of genes to overcome confounding and reverse causality issues in observational studies, by using genetic variants as instrumental variables. Childhood obesity and body mass index (BMI) were exposures and dentofacial anomalies the outcome. After stringent filtering, 14 childhood obesity and 16 BMI related single nucleotide polymorphisms were selected as instrumental variables for analysis using inverse-variance weighted, MR-Egger, weighted median, weighted mode, and Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) methods. To identify potential pleiotropy, the MR-Egger intercept test and the MR-PRESSO global test were applied. Additionally, a leave-one-out sensitivity analysis was conducted to assess the robustness of the findings. **Results**: Childhood obesity (p = 0.005, Odds Radio (OR) = 0.918 [0.865, 0.974]) and higher BMI ($p = 3.72 \times 10^{-6}$, OR = 0.736 [0.646, 0.838]) were associated with reduced risk of dentofacial anomalies, suggesting a potential causal relationship. Cochrane's Q test, funnel plots, Egger intercept test and MR-PRESSO global test showed no heterogeneity or horizontal pleiotropy. Leave-one-out analysis confirmed result stability. **Conclusions**: This study provides genetic evidence that childhood obesity and BMI may be associated with a lower incidence of dental/jaw deformities like malocclusion. While an inverse relationship seems to exist, given overall health risks of childhood obesity, this link warrants cautious interpretation and further research.

Keywords

Childhood obesity; Dentofacial anomalies; Malocclusion; Body mass index; Mendelian randomization

1. Introduction

Dentofacial anomalies encompass a range of conditions affecting dental alignment and jawbone structure, significantly impacting facial appearance. Common forms of these deformities include open bite, underbite, and overbite [1]. These conditions can lead to complications such as difficulty in swallowing, speech issues, and respiratory problems. Furthermore, due to their effect on facial appearance and self-esteem, these deformities often result in social and psychological challenges [2]. Orthodontic treatments for these disorders typically require extended periods and can impose substantial financial burdens [3]. In severe cases, surgical intervention may be necessary. This underscores the importance of researching the pathogenic factors of these deformities and implementing early intervention strategies.

Current research indicates that genetic factors, environmental factors during growth and development, and social behavioral factors play crucial roles in the formation of dentofacial anomalies [4]. Obesity, as a behavioral factor, presents a complex and multifaceted issue in its impact during growth and development, especially in children and adolescents. Some studies have identified a correlation between overweight or obesity and earlier dental development, although not all studies find this difference to be clinically significant [5, 6]. Additionally, research has noted the influence of childhood overweight on bone development [7]. However, to date, there is a lack of

genetic research exploring the relationship between childhood obesity and dentofacial anomalies.

Mendelian randomization (MR) is an epidemiological method that uses genetic variations as instrumental variables [8]. This approach is grounded in Mendel's laws of genetics, positing that the distribution of genetic variations in a population is random. This randomness aids in distinguishing causal relationships between exposures and outcomes, rather than mere correlations. Building on this, the present study aims to investigate the causal relationship between high body weight in childhood and dentofacial anomalies, including malocclusion, by applying a two-sample Mendelian randomization approach.

2. Materials and methods

2.1 Study design

This study employed the two-sample MR approach to explore the causal relationship between exposure and outcome [9]. MR is an epidemiological method that uses genetic variants as instrumental variables (IVs) to assess the causal relationship between exposure factors and outcomes. This method utilizes data from different and independent Genome-Wide Association Studies (GWAS), significantly reducing the likelihood of false positives and enhancing effectiveness and robustness. In this study, Childhood Obesity and Childhood BMI were considered as exposure, while dentofacial anomalies (including malocclusion) were treated as outcome. Single Nucleotide Polymorphisms (SNPs) were selected as instrumental variables for further analysis.

The study adhered to the fundamental principles of MR design and its three key assumptions: (1) All chosen IVs should be highly associated with the exposure; (2) All chosen IVs should be independent of any confounders between the exposure and outcome; (3) All chosen IVs should affect the outcome solely through the exposure, and not *via* any other pathways (as shown in Fig. 1).

2.2 Data collection

Publicly available GWAS databases were searched to obtain qualified exposure and outcome datasets.Considering the potential confounding effect of population admixture on biased estimations, we restricted the population genetic background in our study to individuals of European descent.

The GWAS summary data for Childhood Obesity (ieu-a-1096) were derived from a GWAS meta-analysis [10]. This encompassed 5530 cases (BMI ≥95th percentile) and 8318 controls (BMI <50th percentile) of European individuals. Additionally, to strengthen the evidence, we selected another GWAS meta-analysis dataset for childhood BMI (ebi-a-GCST90002409) as an exposure [11]. This dataset included 61,111 participants and excluded SNPs with a minor allele frequency below 1% and those with poor imputation quality. The outcome GWAS summary data (K11_DENTOFACIAL_ANOMALIES) was obtained from the Finnish database, utilizing the latest R9 version, comprising 9866 cases and 259,234 controls. Due to limitations in the database, clear inclusion criteria for the control group were not provided. Cases were diagnosed with K07 Dentofacial anomalies (including malocclusion) according to the International Classification of Diseases 10th Revision (ICD-10) classification, which primarily encompasses: K07.0 Major anomalies of jaw size; K07.1 Anomalies of jaw-cranial base relationship; K07.2 Anomalies of dental arch relationship; K07.3 Anomalies of tooth position; K07.4 Malocclusion, unspecified; K07.5 Dentofacial functional abnormalities; K07.6 Temporomandibular joint disorders; K07.8 Other dentofacial anomalies; K07.9 Dentofacial anomaly, unspecified (specific diseases included can be referenced at https://icd.who.int/browse10/2019/en#/K07). Detailed information on data sources and availability can be found in **Supplementary Table 1**.

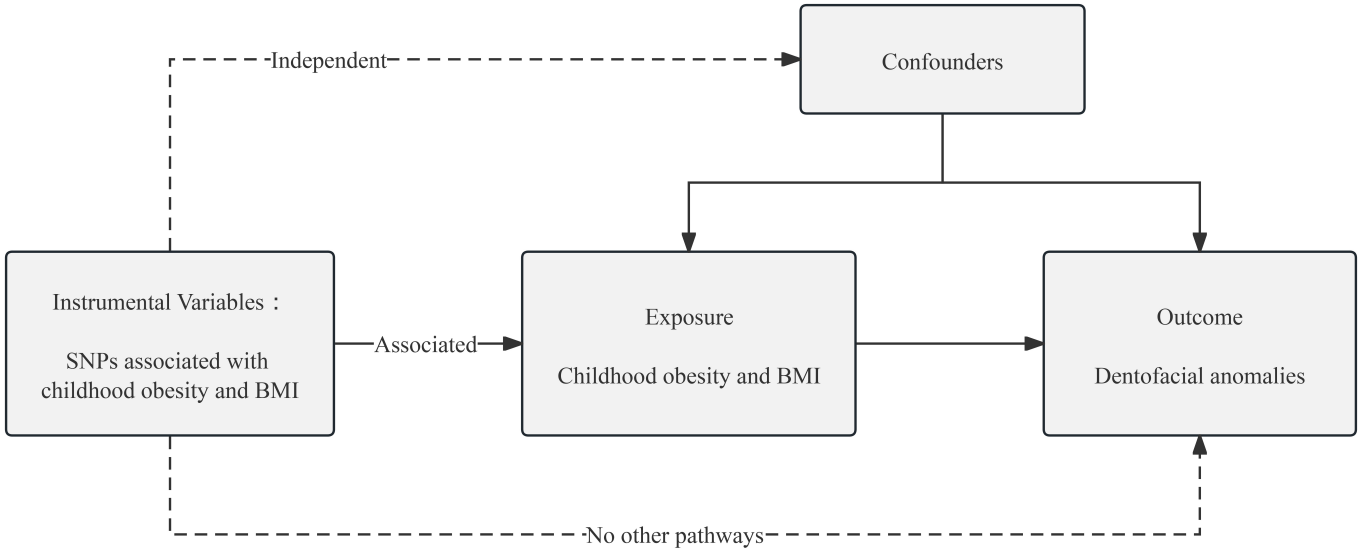


FIGURE 1. Key assumptions of mendelian randomization design. SNPs: Single Nucleotide Polymorphisms; BMI: body mass index.

2.3 Data processing

In this step, we proceed by selecting instrumental variables (IVs) and processing the data format to facilitate further data analysis. In our study, the selection of instrumental variables was guided by the three fundamental assumptions. Firstly, we selected SNPs strongly associated with the exposure ($p < 5 \times 10^{-8}$) and excluded those with an F-value less than 10 to ensure significance and avoid weak IV bias. The F-value formula used in this study is $F = R^2 \times (N - 2)/(1 - R^2)$, where R^2 is the proportion of exposure variance explained by each IV. $R^2 = 2 \times EAF \times (1 - EAF) \times Beta^2$, with Beta being the allele effect size and the effect allele frequency (EAF). Due to missing EAF data in our dataset, we imputed using data from the 1000 Genomes Project [12]. Secondly, to ensure the independence of IVs, a clumping process was conducted because the strong linkage disequilibrium among selected SNPs could lead to biased results. This process ($r^2 < 0.001$, physical window = 10,000 kb) was implemented to ensure IV independence.

Given that only six SNPs could be identified for the Childhood Obesity dataset under the p-value threshold of 5×10^{-8}, a more lenient threshold of $p < 5 \times 10^{-6}$ was employed for this dataset. These SNPs were subsequently verified in the phenotype-wide association study (pheWAS) catalog database to determine if they had potential associations with confounders of the outcome [13]. Finally, to ensure the effect alleles belonged to the same allele, the exposure and outcome datasets were harmonized, and palindromic SNPs and SNPs with indeterminate directionality were removed.

2.4 Statistical analysis

In this study, we explored the relationship between childhood weight and Dentofacial anomalies using five different Mendelian Randomization (MR) methods: inverse-variance weighted (IVW), MR-Egger regression, weighted median, weighted mode, and MR Pleiotropy RESidual Sum and Outlier (MR-PRESSO). IVW, serving as the standard method for summarizing MR data, was used as the primary outcome analysis [14].

The presence of heterogeneity in the associations was revealed using Cochrane's Q test. Additionally, funnel plots were employed to display heterogeneity through their symmetry. The MR-Egger intercept test and the MR-PRESSO global test were used to detect pleiotropy [15]. MR-PRESSO also identifies outliers within the associations and generates estimates after the exclusion of these outliers. Lastly, a leave-one-out sensitivity test was conducted. This method involves the sequential removal of each SNP to observe the effect of the remaining SNPs, thereby examining whether a single SNP with substantial influence might affect the association.

All analyses were carried out using the TwoSampleMR (version 0.5.6) [16] and MR-PRESSO (version 1.0) packages in R, version 4.3.0.

3. Results

3.1 Instrumental variable selection

After stringent criteria-based filtering, a total of 15 SNPs associated with childhood obesity and 17 SNPs linked to childhood BMI were identified. Following the harmonization of exposed and outcome data, 14 SNPs for childhood obesity and 16 SNPs for childhood BMI were selected as IVs for further Mendelian Randomization (MR) analysis. For detailed information about the IVs post-harmonization, refer to **Supplementary Tables 2,3**.

3.2 MR analysis of childhood obesity and dentofacial anomalies

The primary method employed was IVW to investigate the genetic correlation between childhood obesity and dentofacial anomalies. The results indicated that childhood obesity could reduce the risk of dentofacial anomalies ($p = 0.005$, OR = 0.918 [0.865, 0.974]). This association was supported by the weighted median ($p = 0.039$, OR = 0.924 [0.857, 0.996]) and MR-PRESSO ($p = 0.014$, OR = 0.918 [0.865, 0.974]) methods, suggesting a causal relationship. Fig. 2 presents the methodology and results of this MR analysis.

Cochrane's Q test results showed no evidence of heterogeneity in the findings (Q = 16.52, $p = 0.222$). The funnel plot also indicated a symmetrical distribution of SNPs (Fig. 3A). Both the egger intercept test ($p = 0.809$) and the MR-PRESSO global test ($p = 0.263$) demonstrated the absence of horizontal pleiotropy in this association (Table 1). There were no outliers in the MR-PRESSO results within the MR analysis. Furthermore, the leave-one-out test revealed that our MR analysis results were not influenced by any single SNP (Fig. 3B), thus confirming the stability and reliability of these findings.

3.3 MR analysis of childhood BMI and dentofacial anomalies

Similarly, we employed five methods to study the correlation between childhood BMI and dentofacial anomalies. The results of the IVW method indicated that an increase in childhood BMI could reduce the risk of dentofacial anomalies ($p = 3.72 \times 10^{-6}$, OR = 0.736 [0.646, 0.838]). This causal relationship was also supported by the weighted median ($p < 0.001$, OR = 0.711 [0.598, 0.846]), weighted mode ($p = 0.010$, OR = 0.697 [0.548, 0.887]), and MR-PRESSO ($p = 8.36 \times 10^{-5}$, OR = 0.736 [0.657, 0.824]) methods. Fig. 2 presents the methodology and results of this MR analysis.

Cochrane's Q test results showed no evidence of heterogeneity in the findings (Q = 11.29, $p = 0.732$). The funnel plot also indicated a symmetrical distribution of SNPs (Fig. 4A). Both the Egger intercept test ($p = 0.091$) and the MR-PRESSO global test ($p = 0.782$) demonstrated the absence of horizontal pleiotropy in this association (Table 1). There were no outliers in the MR-PRESSO results within the MR analysis. Furthermore, the leave-one-out test revealed that our MR analysis results were not influenced by any single SNP (Fig. 4B), thus confirming the stability and reliability of these findings.

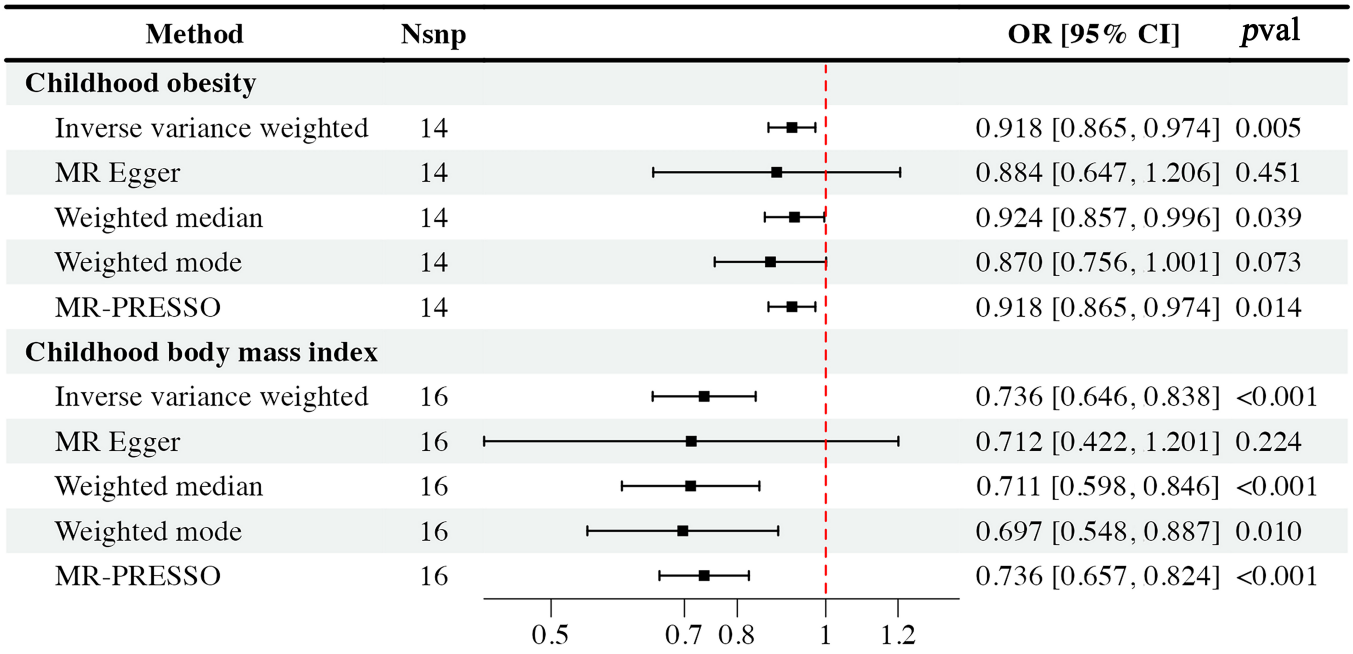


FIGURE 2. Methodology and results of this MR analysis. OR: Odds radio; MR: Mendelian randomization; MR-PRESSO: MR Pleiotropy RESidual Sum and Outlier; CI: Confidence intervals; Nsnp: Number of Single Nucleotide Polymorphisms.

TABLE 1. Analysis of the heterogeneity and pleiotropy of results.

Exposure	Heterogeneity			Pleiotropy	
	Method	Q	*p*	*p* (Egger intercept)	*p* (MR-PRESSO global test)
Childhood Obesity	IVW	16.52	0.222	0.809	0.263
Childhood body mass index	IVW	11.29	0.732	0.901	0.782

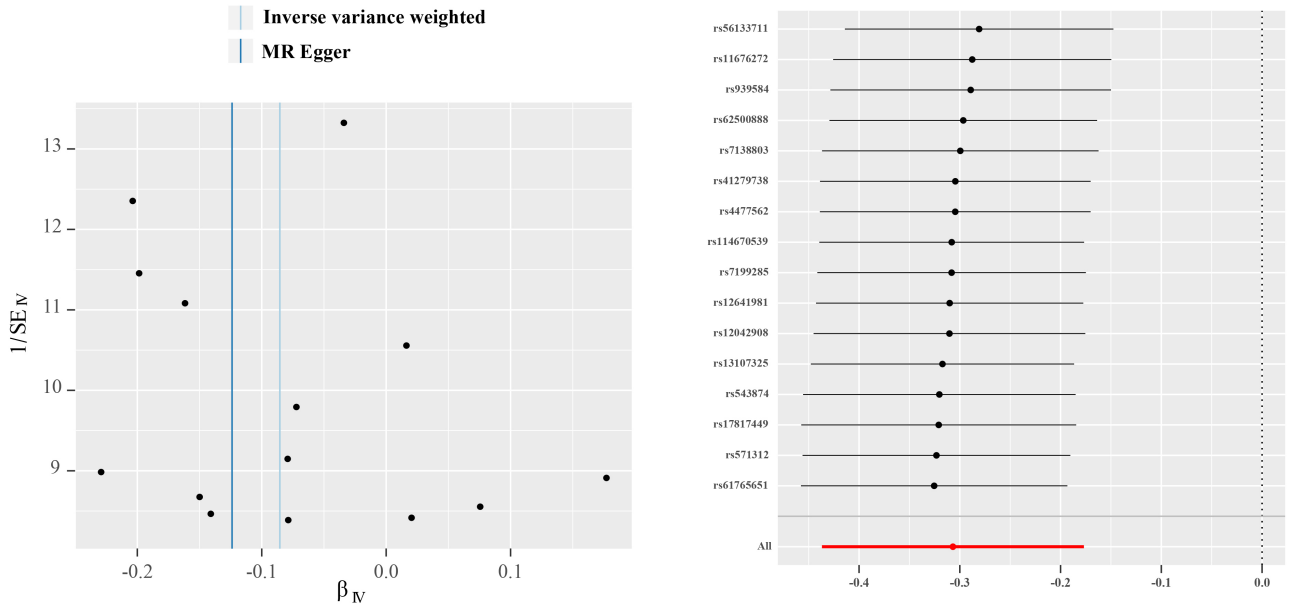
IVW: Inverse variance weighted; MR-PRESSO: Mendelian randomization Pleiotropy RESidual Sum and Outlier.

4. Discussion

This study utilized the bi-sample MR to discover that childhood obesity and higher BMI appear to be associated with a reduced risk of dental and jaw deformities, including malocclusion. This conclusion is consistently supported by various statistical analyses, suggesting a potential causal relationship. This finding could prompt medical researchers and clinicians to explore the potential role of obesity or weight management in preventing and intervening in dentofacial anomalies.

A previous observational study investigated the association between hormonal fingerprints (the ratio of index to ring finger length) and BMI with malocclusion in children [17]. The results indicated that a higher BMI is generally associated with normal dental occlusion and a lower hormonal fingerprint ratio. This study not only supports our findings but also suggests that this outcome may be related to hormonal levels. Furthermore, several related studies have shown that children with higher BMI are more likely to have faster dental development at their age, indicating that BMI has a long-term effect on dental maturation and eruption, which may further relate to occlusal deformities [18, 19]. However, a study has found that in the Indian population, the eruption of teeth may be delayed with the increase of BMI [20]. Additionally, prior research has indicated that overweight and obese adolescents experience earlier craniofacial growth, resulting in larger skeletal dimensions [21]. Another study found that as children's BMI increases, their chewing performance improves, while an increase in Nordic Orofacial Test-Screening (NOT-S) scores is significantly associated with poorer chewing performance [22]. However, this relationship might be influenced by various factors, including psychological aspects like anxiety-driven hunger sensations. Furthermore, studies have also shown that BMI can affect the chewing ability of preschool-aged children [23, 24]. This highlights the complex interplay between psychological and physiological factors in dietary behaviors, suggesting that to fully understand the impact of increased body mass index on craniofacial development and function, both aspects should be considered, which warrants further investigation.

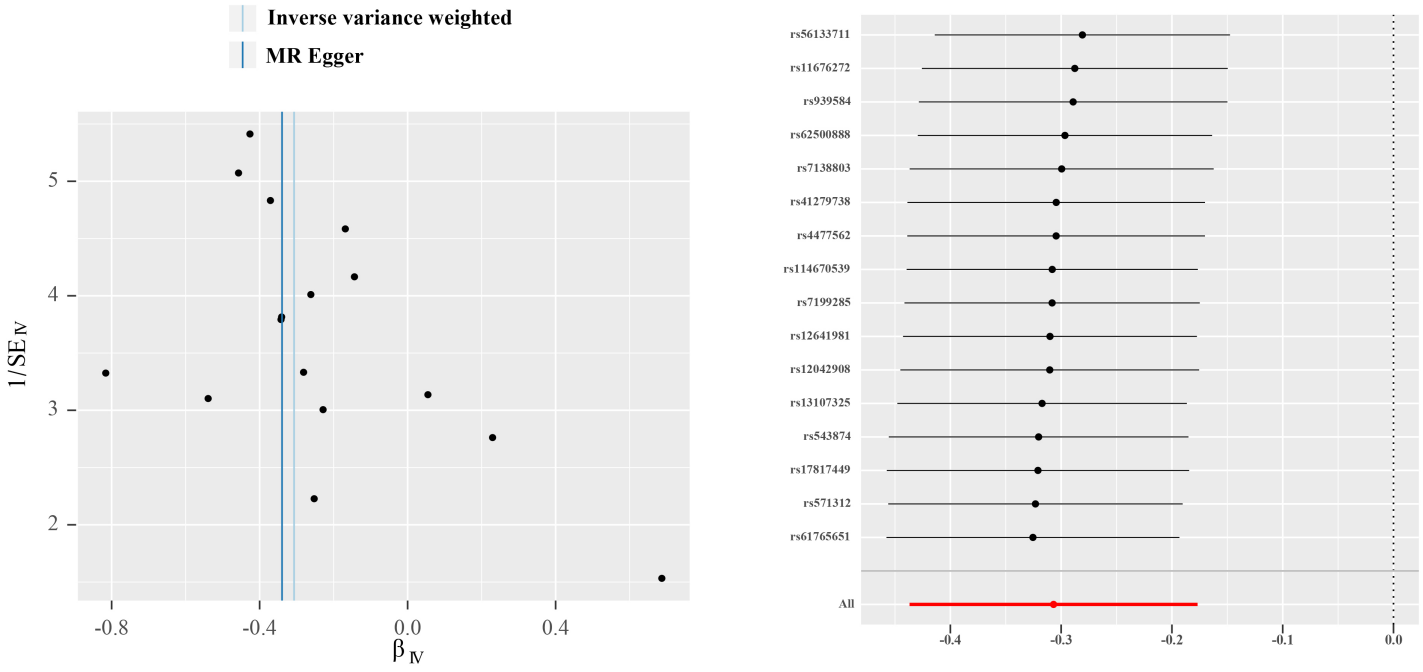
During childhood, weight gain influences growth and development through complex endocrine pathways that affect various hormones and factors. Obesity leads to elevated levels of leptin, a hormone primarily produced by fat cells [25]. Leptin helps regulate energy balance by suppressing hunger and interacts with the hypothalamus, a critical brain region for hormone regulation. This interaction impacts the secretion of Growth Hormone-Releasing Hormone (GHRH), which in turn acts on the pituitary gland to regulate the release of Growth Hormone (GH) [26]. GH stimulates the liver to produce Insulin-like growth factor 1 (IGF-1), promoting growth in bones and other tissues [27]. However, insulin levels are



A: Funnel plot for childhood obesity

B: MR leave-one-out sensitivity analysis for childhood obesity on outcome

FIGURE 3. Funnel plot and Leave-one-out result for the instrumental variables (IVs) of childhood obesity. (A) Funnel plot for the IVs of childhood obesity; (B)Leave-one-out test for the IVs of childhood obesity; MR: Mendelian randomization; SE: Standard error.



A: Funnel plot for childhood body mass index

B: MR leave-one-out sensitivity analysis for childhood BMI on outcome

FIGURE 4. Funnel plot and Leave-one-out result for the instrumental variables (IVs) of body mass index(BMI). (A) Funnel plot for the IVs of BMI; (B) Leave-one-out test for the IVs of BMI; MR: Mendelian randomization; SE: Standard error; BMI: body mass index.

typically elevated in individuals with obesity. Insulin reduces the levels of IGF Binding Proteins 1 and 2 (IGFBP-1 and IGFBP-2), which normally bind IGF-1 in the bloodstream and regulate its bioavailability [28]. With the reduction of IGFBP-1 and IGFBP-2, the bioavailability of IGF-1 increases. Additionally, insulin enhances the effects of IGF-1 by influencing its receptors. Leptin also directly affects the adrenal glands, promoting the secretion of androgens, which can be aromatized into estrogens in adipose tissue [29]. Estrogens can bind to leptin receptors on Estrogen Response Genes and Proteins (EGPs), potentially including various signaling molecules and transcription factors involved in metabolism and growth processes.

This study has several limitations. The genetic data and comprehensive statistical information used were primarily derived from European populations, which may not be applicable to all groups. It is necessary to include cohorts from other populations in further research. Moreover, while there is theoretical and preliminary research suggesting a link between obesity, higher BMI, and a reduced risk of dental and jaw deformities, these findings should be interpreted with caution. Childhood obesity is associated with numerous health issues, including cardiovascular diseases, type 2 diabetes, respiratory problems, and psychosocial issues [30]. Additionally, this study relies on existing datasets and is unable to perform detailed classifications and subgroup analyses of dentofacial anomalies, meaning the study results do not apply to all malocclusions. Moreover, the absence of control group inclusion criteria and data on ages could necessitate further investigation. Therefore, even if there might be an associative effect on certain oral health parameters, this does not mitigate the overall health risks of childhood obesity. To understand this phenomenon more deeply, further research is required to explore the specific impacts of obesity on the craniofacial development of children, particularly its long-term effects. Additionally, management strategies for childhood obesity and oral health should consider multiple aspects of overall health and development.

5. Conclusions

In summary, the research presents genetic and hereditary evidence, obtained through MR, of a causal relationship between childhood obesity or BMI and the development of dentofacial anomalies. Our study indicates that childhood obesity and a higher BMI may reduce the risk of dentofacial anomalies. We highlight the significant role of body weight in craniofacial development, providing critical insights for public health measures and future research directions in this field.

AVAILABILITY OF DATA AND MATERIALS

Childhood obesity GWAS summary (ieu-a-1096): https://gwas.mrcieu.ac.uk/datasets/ieu-a-1096/.

Childhood body mass index GWAS summary (ebi-a-GCST90002409): https://www.ebi.ac.uk/gwas/studies/GCST90002409.

Dentofacial anomalies (including malocclusion) GWAS summary (K11_DENTOFACIAL_ANOMALIES): https://risteys.finregistry.fi/endpoints/K11_DENTOFACIAL_ANOMALIES.

AUTHOR CONTRIBUTIONS

YC and QW—designed the research study; performed the research. XYJ—collected the data. YC and XYJ—engaged in the analysis of the data. YC—wrote the manuscript. XH—reviewed and revised the article. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This research uses publicly available GWAS data and does not require additional ethical approval.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.jocpd.com/files/article/1875053534281383936/attachment/Supplementary%20material.xlsx.

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