

ORIGINAL RESEARCH

Does adolescent obesity influence mandibular development? A mendelian randomization study

Xinwei Zuo¹, Zhengqiang Li², Hongjin Chen², Jin Tang², Wenyue Chen¹, Jiayu Shi², Shuguang Liu^{1,*}

¹Department of Oral and Maxillofacial Surgery, Hospital of Stomatology, Southern Medical University, 510000 Guangzhou, Guangdong, China

²Stomatological Hospital, School of Stomatology, Southern Medical University, 510000 Guangzhou, Guangdong, China

***Correspondence**
dr.liusg@163.com
(Shuguang Liu)

Abstract

Background: Obesity represents a significant determinant impacting children's growth and development; however, its association with craniofacial development remains poorly understood. This study aimed to investigate the causal relationship between obesity and mandibular retrognathia and provide an innovative treatment strategy for dentofacial deformities. **Methods:** Obesity-related genome-wide association study datasets (birth weight, comparative body size at age 10, Body mass index (BMI), whole-body fat mass, body fat percentage, comparative height size at age 10 and standing height) were extracted as instrumental variables for univariate and multivariate Mendelian randomization. Maxillary retrognathia, mandibular retrognathia and mandibular retrognathia (BSSRO) (mandibular retrognathia patients who underwent bilateral sagittal split ramus osteotomy) were analyzed as univariate and multivariate Mendelian randomization (MR) outcomes. The association was assessed using inverse variance weighting (IVW). Furthermore, sensitivity analyses were performed. **Results:** Our univariate MR analysis revealed significant causal risks of mandibular retrognathia (BSSRO) related to comparative body size at age 10 (Odds ratio (OR): 2.039, $p < 0.001$), whole-body fat mass (OR: 1.333, $p = 0.008$) and BMI (OR: 1.341, $p = 0.01$). A significant causal association was found between BSSRO and comparative body size at age 10 (OR: 3.348, $p < 0.001$), whole-body fat mass (OR: 1.767, $p = 0.001$) and BMI (OR: 1.607, $p = 0.006$). Based on multivariate MR analyses, significant causal risk for BSSRO was directly associated with comparative body size at age 10 (multivariate IVW OR: 2.529, $p = 0.016$). Univariate or multivariate MR analyses did not reveal pleiotropy ($p > 0.05$). **Conclusions:** We demonstrated the genetic cause of adolescent obesity in mandibular retrognathia, and proposed a nonsurgical method to treat dental deformities.

Keywords

Mendelian randomization analysis; Mandibular retrognathia; Obesity; Body mass index; Body size; Bilateral sagittal split ramus osteotomy

1. Introduction

Dental-maxillofacial deformities remain globally significant. A recent meta-analysis reported prevalence rates of 51.9% for Class I, 23.8% for Class II and 6.5% for Class III malocclusions [1]. According to the World Dental Federation (FDI), malocclusions can result in dental caries, periodontitis and occlusal trauma, as well as abnormalities in chewing, swallowing, breathing and speech. Physical and mental health can also be affected by malocclusions, affecting facial appearance, psychological well-being and impacting patients' quality of life. Furthermore, it burdens the global economy heavily.

Angle Class II malocclusion patients are primarily classified based on dental and skeletal abnormalities. Orthodontic treatment alone often results in favorable outcomes for patients with Angle's Class II malocclusions with no significant developmental malformations. Typically, patients with

class II skeletal patterns malocclusion, specifically mandibular retrognathia, have underdeveloped mandibles. The condylar process, serving as the center of development, is frequently notably underdeveloped and accompanied by various structural abnormalities in the joint and anomalies in the masticatory muscle group, leading to temporomandibular disorders (TMD) [2, 3]. Concurrently, mandibular underdevelopment can predispose to airway stenosis and sleep apnea syndrome [4, 5]. Patients with these conditions benefit only from orthodontic treatment masking effects. The most common treatment for skeletal class II mandibular retrognathia is combined joint-orthodontic-orthognathic surgery to improve occlusion, alleviate joint burdens, increase airway volume and alter facial appearance. According to statistics, orthognathic surgery prevalence in Sweden from 2010 to 2014 was 6.3 cases per 100,000 people [6]. In 2008, 10,345 orthognathic surgeries were conducted in the United States, at an average cost of

\$47,348 per procedure [7]. As dentofacial deformities are prevalent and orthognathic surgery is burgeoning [8, 9], it is expected that an increasing number of patients with such deformities will undergo orthognathic procedures in the future. However, orthognathic surgery still has several limitations: (1) It involves greater surgical trauma and increased bleeding. (2) Preoperative design complexity, surgical difficulty, risk and technical demands are high. (3) The prolonged recovery period has a significant impact on the patient's daily life and work. (4) Standardized joint-orthodontic-orthognathic combined treatment is associated with a lengthy treatment cycle, necessitates collaboration among multiple healthcare professionals, and can be costly. (5) The unstable temporomandibular joint state easily caused by an underdeveloped condyle in Class II patients may lead to recurrence after surgery [10, 11]. (6) Our previous study found that half a year after bilateral sagittal split ramus osteotomy (BSSRO), condylar absorption in Class II patients reached 83.33%, and the condylar volume absorption rate was 10.51%. Sleep apnea syndrome caused by mandibular retrognathia could often be relieved after surgery [12].

As orthognathic surgery comes with increased risks and complexities, early intervention methods are essential for managing mandibular retrognathia. While genetic and complex environmental factors play a significant role in mandibular retrognathia, its etiology remains unclear [13–15]. Furthermore, obesity is a significant factor among these factors. Obesity is a critical factor influencing children's growth and development [16–19], with 19.7% of children and adolescents aged 2 to 19 affected [20]. We hypothesize that obesity may increase mandibular retrognathia risk. However, research on obesity's effects on maxillary and mandibular development is limited. Studies suggest that obesity accelerates jaw and tooth development [21–24], but evidence regarding its potential to restrict maxillary and mandibular growth remains sparse. We therefore intend to determine whether early intervention in adolescent obesity can reduce the incidence of mandibular retrognathia, thus focusing on obesity throughout life.

2. Materials and methods

2.1 Study design

MR is based on Single Nucleotide Polymorphisms (SNPs) as instrumental variables. The study must comply with three basic MR principles. The first principle necessitates a strong correlation between the instrumental variables (IVs) and the exposure factor of interest, allowing it to serve as a proxy for the exposure factor. According to the second principle, IVs should be independent of confounding factors for both exposure and outcome, thus eliminating indirect exposure effects. Thirdly, the IVs should not show any correlation with the outcome variable. In this MR study, data from published articles were used, eliminating ethical approval (Fig. 1). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization (STROBE-MR) guideline [25, 26]. All MR analyses were conducted using R (version 4.3.2) with the TwoSampleMR package (version 0.5.8) and the Mendelian Randomization package (version 0.9.0).

2.2 Data source

We accessed the summary statistics exposure dataset from the Integrative Epidemiology Unit (IEU) OpenGWAS project website (<https://gwas.mrcieu.ac.uk>), which includes Genome-wide association study (GWAS) data on birth weight, comparative body size at age 10, BMI, standing height, body fat percentage, whole body fat mass and comparative height at age 10. The outcome dataset was also accessed from the FinnGen database (<https://r12.finnngen.fi/>), which contains information on maxillary retrognathia, mandibular retrognathia and mandibular retrognathia (BSSRO) (patients who underwent bilateral sagittal split ramus osteotomy). Exposures and outcomes were collected from two different European populations. The data description was as follows: birth weight data were obtained through interviews with participants who provided medical measurement results at birth. Comparative body size at age 10 and comparative height at age 10 were based on participant recall regarding their average size compared to others at age 10, indicating whether they were “thinner/shorter”, “fuller/taller” or “average”. Weight was divided by height squared to calculate BMI. Bioelectrical impedance analysis and dual-energy X-ray absorption were used to determine body fat percentage and whole-body fat mass. Patients diagnosed with maxillary retrognathia, mandibular retrognathia and mandibular retrognathia (BSSRO) were identified based on the updated International Classification of Diseases (ICD-10) codes (Table 1).

2.3 Instruments selection

As instrumental variables, qualified SNPs associated with lifelong obesity were selected using the following steps. First, SNPs significantly associated with the exposure ($p < 5 \times 10^{-8}$) were included. IVs were then clustered, and the independent SNPs with the lowest p -value ($r^2 \geq 0.001$, clustering window $\leq 10,000$ kb) were retained. Simultaneously, the PhenoScanner V2 website (<https://www.repository.cam.ac.uk/items/31e4df31-982b-452e-baf8-83ce942b1c0a>) was used to exclude SNPs related to potential confounding factors (growth and development disorders, education level, dietary habits, *etc.*) and SNPs related to the outcome. Using specific tools, R^2 and F statistics for each instrumental variable were calculated. $F = \frac{R^2}{1-R^2} \times \frac{N-K-1}{K}$, standard deviation (SD) = standard error (SE) $\times \sqrt{N}$. SNP's F statistics > 10 , the SNP was generally considered to be a strong tool. Next, we extracted the exposure SNPs from the outcome variable data set and deleted any SNP that showed a significant association with the outcome variable ($p < 5 \times 10^{-8}$). To obtain the final IVs, we harmonized the remaining exposure and outcome SNPs to ensure compatibility and deleted any ambiguous or incompatible SNPs.

2.4 Statistical analysis

The inverse-variance weighted (IVW) method, weighted median (WM) method and MR-Egger method were used in univariate MR. For multivariate MR, both the IVW and MR-Egger methods were used. Both MR approaches used the

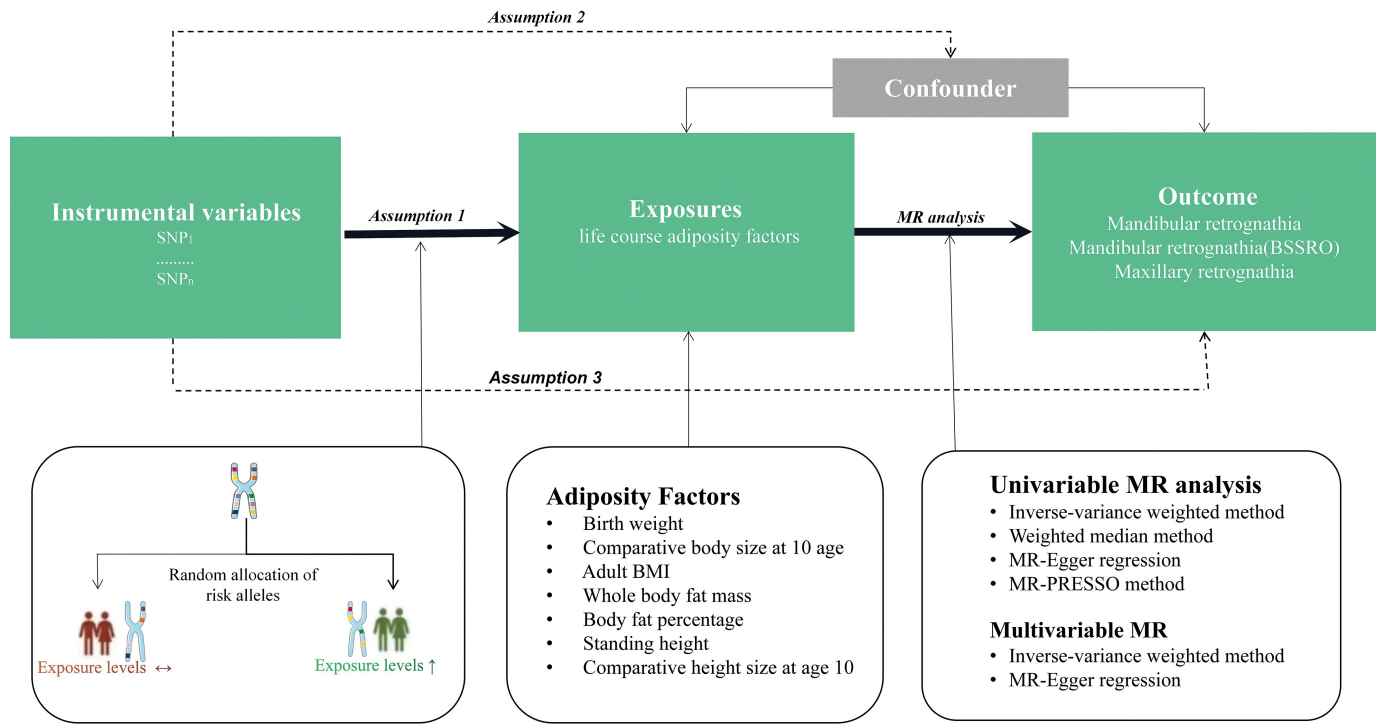


FIGURE 1. Schematic design of Mendelian randomization. Mendelian randomization requires that the effective genetic instrumental variation satisfies three assumptions. SNP: Single nucleotide polymorphism; MR: Mendelian randomization; BMI: Body mass index; MR-PRESSO: Mendelian Randomization Pleiotropy RESidual Sum and Outlier; BSSRO: Bilateral Sagittal Split Ramus Osteotomy.

TABLE 1. Details of data sources used in this study.

Traits	Year	Authors	Population	Consortium	Sample size	Number of SNPs
Birth weight	2018	Ben Elsworth	European	MRC-IEU	261,932	9,851,867
Body mass index (BMI)	2017	Neale	European	Neale Lab	336,107	10,894,596
Comparative body size at age 10, males and females	2020	Richardson	European	/	453,169	12,321,879
Whole body fat mass	2018	Ben Elsworth	European	MRC-IEU	454,137	9,851,867
Body fat percentage	2018	Ben Elsworth	European	MRC-IEU	454,633	9,851,867
Standing height	2018	Ben Elsworth	European	MRC-IEU	461,950	9,851,867
Comparative height size at age 10	2017	Neale	European	Neale Lab	332,021	10,894,596
Mandibular retrognathia and surgery (BSSRO)	2024	Kurki	European	FinnGen	764	21,306,347
Mandibular retrognathia	2024	Kurki	European	FinnGen	1965	21,306,347
Maxillary retrognathia	2024	Kurki	European	FinnGen	510	21,306,347

Notes: mandibular retrognathia AND surgery (BSSRO) as described in the article mandibular retrognathia (BSSRO). BSSRO: Bilateral Sagittal Split Ramus Osteotomy; MRC-IEU: MRC Integrative Epidemiology Unit.

IVW method as their primary analysis. We pooled Wald ratios for each SNP, using the WM method and MR-Egger as supplementary analyses. Significance was inferred when the direction of estimates from both methods was consistent with IVW. Outlier SNPs identified by Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) were removed, and the MR analysis was repeated. For univariate MR, five phenotypes representing obesity at different life stages were selected. Statistical significance was determined using the Bonferroni correction at a p -value of 0.01 (0.05/5). Asso-

ciations with a p -value between 0.01 and 0.05 were considered suggestive evidence. To assess the robustness of the study's findings, sensitivity analyses were conducted. Cochran's Q test was conducted to evaluate heterogeneity across IVs. For all analyses, a random effects model was used. The MR-Egger intercept test, Mendelian randomization pleiotropy residual sum and outliers (MR-PRESSO), and leave-one-out (LOO) analysis were used to detect horizontal pleiotropy.

3. Results

3.1 The main results of the MR analyses

Univariate MR analysis indicated that prepubertal obesity and adult adiposity may increase the risk of mandibular retrognathia and mandibular retrognathia (BSSRO). However, no significant association was found with maxillary retrognathia (Fig. 2). In multivariate MR analyses, the effect of obesity in prepuberty was found to be directly associated with mandibular retrognathia (Fig. 3).

3.2 Univariate MR

Significant causal risk of mandibular retrognathia was associated with comparative body size at age 10 (OR: 2.039, 95% CI: 1.336–3.112, $p < 0.001$), whole-body fat mass (OR: 1.333, 95% CI: 1.074–1.654, $p = 0.008$) and adult BMI (OR: 1.341, 95% CI: 1.072–1.677, $p = 0.01$). Significant causal risk of mandibular retrognathia (BSSRO) was associated with comparative body size at age 10 (OR: 3.348, 95% CI: 1.811–6.701, $p < 0.001$), whole-body fat mass (OR: 1.767, 95% CI: 1.245–2.509, $p = 0.001$) and adult BMI (OR: 1.607, 95% CI: 1.141–2.262, $p = 0.006$). These results are in agreement with those obtained from the MR-Egger and WM methods (Supplementary Figs. 1,2,3). However, neither birth weight nor body fat percentage were associated with mandibular retrognathia or BSSRO ($p > 0.05$). Similarly, no causal relationship between obesity-related exposures and maxillary retrognathia was found ($p > 0.05$).

The Cochran Q test analysis indicated heterogeneity among IVs related to birth weight, comparative body size at 10, BMI and whole-body fat mass in BSSRO. Other than birth weight (28.4%), all I^2 values were $<25\%$, suggesting low

heterogeneity (Table 2) while using the random-effects IVW method could reduce bias. IVs in BSSRO and maxillary retrognathia showed no heterogeneity. The MR-Egger intercept provided no evidence of pleiotropy ($p > 0.05$), and MR-PRESSO did not identify outlier SNPs. LOO analysis showed that no single SNP contradicted obesity-related mandibular retrognathia (Supplementary Figs. 4,5,6). The funnel plot displayed symmetry (Supplementary Figs. 7,8,9).

3.3 Multivariable MR

A multivariable MR analysis of mandibular retrognathia identified 1027 independent SNPs as IVs associated with birth weight, comparative body size at age 10, BMI, comparative height size at age 10 and standing height. Mandibular retrognathia is directly associated with comparative body size at age 10 (OR: 2.529, 95% CI: 1.186–5.39, $p = 0.016$). However, there was limited evidence of the direct correlation between mandibular retrognathia and birth weight (OR: 0.949, 95% CI: 0.602–1.496, $p = 0.824$), comparative height and size at age 10 (OR: 0.804, 95% CI: 0.312–2.07, $p = 0.652$), BMI (OR: 0.877, 95% CI: 0.542–1.422, $p = 0.596$) and standing height (OR: 1.103, 95% CI: 0.545–2.231, $p = 0.783$). The MR-Egger analysis revealed a significant direct effect of comparative body size at age 10 on mandibular retrognathia risk ($p = 0.013$), in agreement with the IVW findings. The sensitivity analysis using Cochran's Q test revealed heterogeneity in IV effect estimates ($p = 1 \times 10^{-4}$), with a Cochran's Q statistic of 813.069 and $I^2 = 16.1\%$. Heterogeneity was present, but it was deemed small. A random-effects IVW analysis was then conducted to mitigate heterogeneity. MR-Egger's intercept did not indicate pleiotropy ($p = 0.453$).

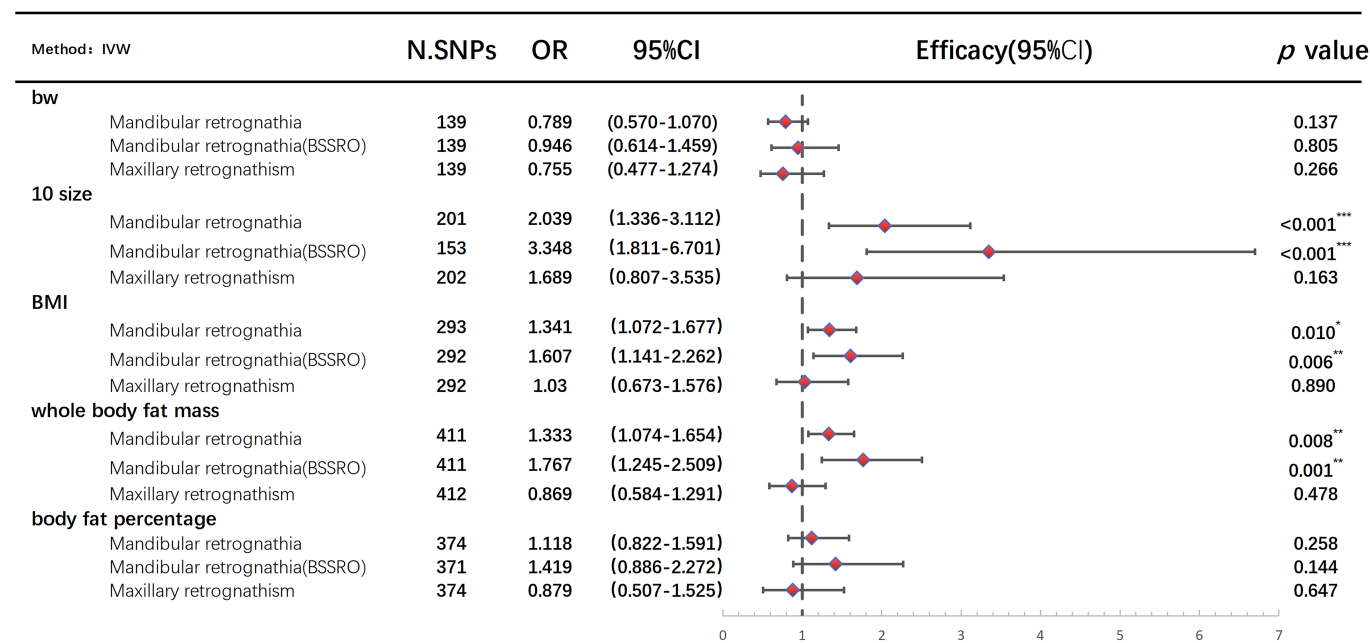


FIGURE 2. Forest plot of IVW of MR analysis describing genetic life obesity tool genes and mandibular retrognathia, mandibular retrognathia (BSSRO), and maxillary retrognathia. N.SNPs: number of SNPs used in MR; OR: odds ratio; CI: confidence interval; IVW: inverse variance weighting; 10 size: comparative body size at age 10; bw: birth weight; BMI: Body mass index; BSSRO: Bilateral Sagittal Split Ramus Osteotomy. “*” for $p < 0.05$; “**” for $p < 0.01$; “***” for $p < 0.001$.

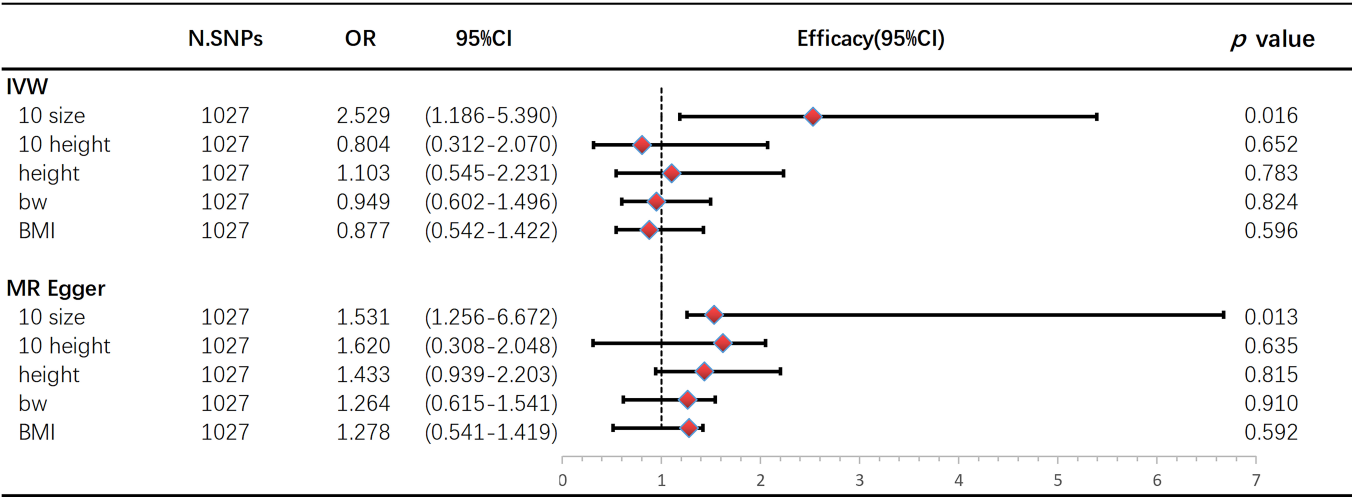


FIGURE 3. Multivariate MR to assess the association of corrected birth weight, prepubertal body size, prepubertal height, body mass index in adulthood and adult height with mandibular retrognathia. OR: odds ratio; CI: confidence interval; IVW: inverse variance weighted; 10 size: comparative body size at age 10; 10 height: comparative height size at age 10; bw: birth weight; BMI: Body mass index; N.SNPs: number of SNPs used in MR.

TABLE 2. Sensitivity analysis of univariate MR between life-cycle obesity and mandibular retrognathia, mandibular retrognathia (BSSRO) and maxillary retrognathia.

Exposure	Cochran Q test			MR-Egger	
	Q value	I ²	p-value	Intercept	p-value
Mandibular retrognathia					
bw	138	0.284	0.001	0.001	0.867
10 size	200	0.230	0.002	-0.007	0.287
BMI	292	0.160	0.012	-0.010	0.145
Whole body fat mass	463	0.118	0.030	-0.007	0.195
Body fat percentage	412	0.094	0.075	-0.011	0.079
Mandibular retrognathia (BSSRO)					
bw	145	0.053	0.310	0.007	0.628
10 size	133	0.125	0.859	-0.011	0.248
BMI	317	0.083	0.130	-0.005	0.630
Whole body fat mass	480	0.147	0.009	-0.012	0.157
Body fat percentage	409	0.092	0.080	-0.020	0.059
Maxillary retrognathia					
bw	141	0.024	0.403	-0.001	0.934
10 size	208	0.034	0.349	0.003	0.743
BMI	326	0.107	0.076	-0.008	0.383
Whole body fat mass	384	0.070	0.825	-0.008	0.383
Body fat percentage	374	0.005	0.462	-0.020	0.054

Notes: bw: birth weight; MR: Mendelian randomization; BMI: Body mass index; 10 size: comparative body size at age 10; BSSRO: Bilateral Sagittal Split Ramus Osteotomy.

4. Discussion

This study is the first to use both univariate and multivariate MR methods based on GWAS data to investigate the causal relationships between various obesity phenotypes throughout life and mandibular retrognathia. Based on a univariate MR analysis, comparative body size at age 10, whole body fat mass and BMI are risk factors for mandibular retrognathia. No significant effect was observed on body fat percentage and birth weight in mandibular retrognathia. These findings were in

accordance with the univariate MR analysis of mandibular retrognathia (BSSRO). Maxillary retrognathia was not causally related to obesity-related characteristics in a univariate MR analysis. According to multivariate MR analysis, comparative body size at age 10 was primarily responsible for mandibular retrognathia, with no evidence of indirect effects from other obesity-associated factors. Childhood obesity has been linked to long bone problems in previous studies. However, the mandibular and maxilla have received less attention. Clinical

work could be guided by these findings to improve our understanding of mandibular retrognathia.

In our study, we selected self-reported comparative body size at age 10 as an indicator of preadolescence obesity, and birth weight as a supplementary indicator of childhood obesity. Jaw development restriction is not associated with obesity before puberty. In clinical practice, genetic factors and unhealthy habits have gained more attention. Previous studies have shown that obesity may accelerate facial development [24], resulting in a larger facial size at the same age [27], which aligns with its effect on overall growth. Numerous clinical studies have demonstrated that obesity in early adolescence is associated with precocious puberty. Obese children tend to have increased height, approaching adult levels in organ development [28, 29]. Prepubertal obesity, however, was not associated with restricted maxillary development but rather restricted mandibular development in both univariate and multivariate MR analyses. Previous research has not entirely supported this finding. A plausible explanation could be the different histological properties of jaw bones compared to long bones. Additionally, the maxilla and mandible differ histologically. There is variability in growth characteristics and developmental trajectories between trunk bones and craniofacial structures, as well as between the maxilla and mandible.

Mandibular retrognathia caused by adolescent obesity may be related to abnormal growth and development hormone metabolism. Obesity-induced abnormal hormone regulation could contribute to mandibular retrognathia. Leptin, secreted by adipose tissue, plays a crucial role in body growth and development [30]. Children with obesity exhibit a significant growth pattern that is influenced by interactions between leptin and kisspeptin [31, 32]. According to animal experiments, leptin may significantly influence craniofacial growth and morphology [33]. Leptin resistance could impede mandibular development. Leptin also enhances muscle strength. There is increased development of muscles surrounding the temporomandibular joint in obese adolescents. Therefore, robust soft tissue traction forces can hinder mandibular development, potentially delaying mandibular length development. The mandibular rotation around the terminal molar may also be counter-clockwise, exacerbating mandibular retrognathia [34, 35]. Changes in plasma concentrations of sex steroids, growth hormone and insulin-like growth factor-I (IGF-I) caused by obesity can also lead to mandibular retrognathia [36, 37]. Gonadal steroid hormones play a crucial role in normal pubertal growth spurts and bone development. Increased levels of leptin and sex hormones in obese children can accelerate epiphyseal maturation and skeletal pubertal growth, which promotes mandibular development [38]. Animal studies have demonstrated that pubertal estrogens significantly influence skull morphology [39, 40]. With increasing BMI, testosterone levels decrease, resulting in a decrease in mandibular and condyle growth [41]. Growth hormone regulation has a more significant impact on mandibular development than on maxillary development [42]. Numerous studies have demonstrated that growth hormone-related genes significantly affect craniofacial bone growth [17, 43, 44]. Growth hormone therapy can increase mandibular length [45, 46].

Different developmental characteristics, inconsistent development time, and speed of the maxilla and mandible, obesity could result in abnormal bone metabolism leading to mandibular retrognathia [47]. During puberty, the body undergoes substantial skeletal growth and development, including the length and width of the mandible and the temporomandibular joint. Mandibular condyles provide endochondral ossification and contribute to mandibular height. Direct bone deposition and resorption on the bone surface also increases the length and depth of the mandible. For suture growth and bone surface proliferation, the maxilla contributes length, width and depth. Growth stimuli stimulated by skull base development also influence the development of the mandible and maxilla [48]. Cartilage growth persists throughout adolescence in alignment with overall body growth and development during adolescence [49]. Consequently, facial width development during adolescence is shorter than that of facial depth and height. Additionally, facial height growth is greater than in-depth, which is greater than width. Surface bone hyperplasia is transient and heavily influenced by precocious puberty resulting from obesity in preadolescence and hormonal growth and development disorders. This subsequently impacts mandibular width and depth, contributing to mandibular retrognathia. Continual posterior and superior growth of the condyle can cause mandibular rotation, exacerbating mandibular retrognathia. The suture growth and early development time of maxilla results in little effect of obesity on maxillary development during adolescence [50], which is in line with our findings.

We selected BMI as an indicator of obesity in adulthood, and whole-body fat mass and body fat percentage as supplementary indicators of adulthood obesity. Li *et al.* [51] found that childhood obesity is associated with an increased risk of early puberty. Because whole body fat mass and body fat percentage are more sensitive to early puberty than BMI, we chose them as exposure factors. According to our study, high BMI and whole-body fat mass are risk factors for mandibular retrognathia in adults, but not body fat percentage. We suggest that the association between obesity in adulthood and mandibular retrognathia is related to obesity's residual effects during jaw development. Multivariate MR analysis confirms this finding. There is a strong correlation between adult obesity and childhood obesity [52]. Observational studies have found that childhood obesity is closely related to adult obesity, and obese adolescents are more likely to remain obese in adulthood [53]. Generally, childhood obesity results from an increase in both the number and size of adipocytes. After the body reaches maturity in adolescence, the number of adipocytes established during childhood is maintained into adulthood, with adult obesity primarily resulting from an increase in adipocyte size. While we used whole-body fat mass as an adult index, a high whole-body fat mass may indicate a higher adipocyte content in childhood [54]. The close relationship between adipocytes and jaw development may explain the association between total fat content and mandibular retrognathia.

Within the framework of multivariate MR analysis, our study further revealed that, after adjusting for birth weight, comparative height at age 10, and BMI, comparative body size at age 10 was a direct risk factor for mandibular retrognathia. In contrast, the association between BMI and whole-

body fat mass content decreased in adults. According to biological characteristics, BMI affects mandibular retrognathia over the life course. In early adolescence, high BMI may hinder the development of the temporomandibular joint (TMJ) and mandible. In adulthood, the associated structures are mature, reducing the effect of BMI on mandibular retrognathia. Further, BMI may influence mandibular retrognathia in a different way than obesity in preadolescence. Adults may be more susceptible to socioeconomic and competitive pressures. Through temporomandibular joint remodeling and resorption, this could have a greater effect on mandibular retrognathia. During adolescence and childhood, obesity may affect jaw development in adults.

For young patients with mandibular retrognathia seeking orthodontic and orthognathic treatment, it is essential to routinely monitor body shape, weight and history of adolescent obesity. These parameters assist in evaluating the risk of mandibular retrognathia and are crucial for assessing TMD and pediatric sleep apnea syndrome associated with mandibular retrognathia. Regular observation of jaw development and early intervention are recommended. However, according to an online survey of approximately 7450 pediatric dentists and dental residents, only 17% offer childhood obesity interventions [55]. Among 1046 respondents randomly selected from 13,357 dental care workers, 91% never measured patients' height and weight and 94% never measured BMI [56]. Dentists should expand their scope of patient care to include weight assessment and management, focusing not only on oral health but also on the impact of systemic health. A multidisciplinary approach is essential for the effective management of adolescent obesity and mandibular retrognathia. Close collaboration among dentists, pediatricians, nutritionists, and other healthcare professionals is necessary to address the complex interplay between obesity and the development of mandibular.

Our MR study supports a causal relationship between preadolescent obesity and mandibular retrognathia. The IVW approach used in MR assumes the validity of all IVs and may be susceptible to bias from pleiotropic effects [57]. Additionally, we applied the WM, which provides consistent estimates even when at least half of the IVs are invalid. We used the MR-Egger method, which assumes that all instrumental variables are invalid. Importantly, all MR methods produced consistent results. Supplementary statistical methods did not find a horizontal pleiotropy. The results for mandibular retrognathia and mandibular retrognathia (BSSRO) were consistent, which makes our conclusions more robust. Additional MR analysis of maxillary retrognathia also suggested an association with obesity, since it was associated only with restricted mandibular growth. The results of this study should be interpreted with caution due to several limitations. First, because this study focused on Europeans, its conclusions apply only to them. Second, incomplete control of confounding factors may result in biased and inaccurate results. Although the SNPs used in the MR analysis were adjusted for TMJ disease, facial and systemic growth and development disorders, and conditions such as anxiety, tension, genetics of hormone metabolism, TMD and education level, other important confounding factors may not have been adequately addressed. Third, some of the IVs selected in this study exhibited heterogeneity, but it was

minimal. A random effects IVW model was used for statistical analysis, which minimized any insignificant influence on the outcomes [58, 59]. Fourth, preadolescence obesity data were assessed subjectively in this study, introducing potential bias. Fifth, mandibular retrognathia is primarily caused by genetic factors. However, it may also result from acquired factors such as contrecoup injury to the chin during jaw development, mandibular fractures, and condylar fractures. The development of the mandible can also be hindered by certain childhood habits, such as hand-dragging the chin. Sixth, the effect of obesity on mandibular retrognathia may exist only during a critical period. MR estimates could be misleading if used to guide future interventions if they occur outside of this time frame. To elucidate the mechanisms behind mandibular retrognathia, additional studies are needed. Finally, MR is capable of exploring causal relationships, but practical clinical implications must be approached cautiously. For a better understanding of the specific mechanisms affecting maxillofacial development, more high-quality clinical studies are needed to validate the impact of early adolescent obesity on mandibular retrognathia.

5. Conclusions

Prepubertal obesity is a direct risk factor for mandibular retrognathia, underscoring the importance of nutrition and weight management during early adolescence to prevent mandibular retrognathia. In providing medical advice to patients with mandibular retrognathia, dentists should emphasize the importance of weight monitoring and management, especially for those who have experienced or are experiencing prepubertal obesity.

ABBREVIATIONS

BMI, Body mass index; BSSRO, Bilateral Sagittal Split Ramus Osteotomy; MR, Mendelian randomization; IVW, Inverse variance-weighted; OR, Odds ratio; FDI, World Dental Federation; TMD, Temporomandibular Disorder; SNPs, Single nucleotide polymorphisms; IVs, Instrumental variables; STROBE-MR, Strengthening the Reporting of Observational Studies in Epidemiology-Mendelian Randomization; IEU, Integrative Epidemiology Unit; GWAS, Genome-wide association study; ICD, International Classification of Diseases; WM, weighted median; SD, standard deviation; SE, standard error; MR-PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; LOO, leave-one-out; N.SNPs, number of SNPs used in MR; CI, Confidence interval; 10 size, comparative body size at age 10; bw, birth weight; 10 height, comparative height size at age 10; IGF-I, insulin-like growth factor-I; TMJ, Temporomandibular Joint.

AVAILABILITY OF DATA AND MATERIALS

Data is provided within the manuscript or supplementary information files. GWAS data are available from the following links: (<https://gwas.mrcieu.ac.uk>) and (<https://r12.finngen.fi/>).

AUTHOR CONTRIBUTIONS

XWZ—conceptualization, methodology, writing—original draft, software, formal analysis. ZQL—investigation, formal analysis, software, visualization, writing—original draft. JT—methodology, writing. WYC—methodology, investigation. HJC—methodology, validation. JYS—methodology, software. SGL—investigation, validation and supervision.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All the data in our study were obtained from large-scale GWASs, Informed consent was obtained from all participating patients. So the study does not require 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/1985215967725010944/attachment/Supplementary%20material.docx>.

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