Diabetes, Metabolic Syndrome and Obesity

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REVIEW

Advances in Mendelian Randomization Studies of Obesity Over the Past Decade: Uncovering Key Genetic Mechanisms

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Abstract: Obesity is a major global public health issue linked to a wide range of chronic diseases. Understanding its complex causal pathways requires robust analytical methods. Mendelian randomization (MR), which employs genetic variants as instrumental variables, effectively addresses confounding and reverse causation and has become a key tool in obesity research. This review summarizes the development of MR methodologies, from single-sample to multivariable, mediation, and time-series models, and highlights key findings from the past decade. MR studies have revealed causal associations between obesity and nine major disease categories, including cardiovascular, metabolic, cancer, psychiatric, respiratory, renal, reproductive, musculoskeletal, and dermatological disorders. Obesity influences disease risk through mechanisms involving energy metabolism, hormonal regulation, and inflammation, with heterogeneity by age, sex, and fat distribution. Key genes such as *MC4R, LEPR, FTO*, and *FGF21* have been identified as potential therapeutic targets. Current challenges include instrument strength, pleiotropy, population stratification, and the external validity of GWAS data. Future research that integrates multi-ancestry GWAS, functional validation, and multi-omics approaches may further enhance the utility of Mendelian randomization. MR provides a robust genetic framework for elucidating obesity's causal effects and informing targeted interventions and personalized treatment strategies.

Keywords: Mendelian randomization, obesity, genetic variation, research progress

Introduction

With rapid economic development in China, obesity has become a major public health concern, with more than half of adults classified as overweight or obese.[1] The World Health Organization (WHO) defines obesity as excessive fat accumulation that may impair health,[2] and it constitutes a key component of metabolic syndrome.[3] Obesity can be quantified using indicators such as body mass index (BMI), waist circumference, and waist-to-hip ratio. According to WHO BMI classifications, overweight is defined as a BMI of 25.0–29.9 kg/m², obesity as ≥30 kg/m², and severe obesity as ≥40 kg/m².[4] The development of obesity is influenced by a complex interplay of genetic factors, environmental exposures, and gene-environment interactions. Although numerous clinical studies have demonstrated that obesity significantly increases the risk of metabolic diseases, cardiovascular diseases, musculoskeletal disorders, psychiatric conditions, and various cancers,[5] the causal nature of these associations remains unclear due to potential confounding and reverse causation.

To address these limitations, researchers have increasingly adopted Mendelian randomization (MR), a method that uses genetic variants associated with obesity to infer causal effects on disease outcomes. Often described as a "natural randomized controlled trial (RCT)", MR leverages the random allocation of genetic variants at conception, providing stable and unbiased exposure measures. This minimizes confounding and reverse causation, enabling more robust causal inference. The application of MR in obesity research has evolved significantly, progressing from single-sample analyses

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to multi-sample approaches and integrating mediation analysis and temporal modeling. These methodological advances allow researchers to explore the causal pathways linking obesity to various diseases under diverse contexts. This review systematically examines the methodological evolution of MR over the past decade and highlights key genetic discoveries in obesity research, aiming to provide a genetic foundation for the development of targeted therapies for obesity and its related conditions.

Principles and Methodology of Mendelian Randomization

Mendelian randomization (MR) is a statistical approach based on large-scale genome-wide association study (GWAS) data, widely used in epidemiology to infer causal relationships between exposures and disease outcomes. Originally proposed by Katan in 1986,[6] MR leverages Mendel's second law of inheritance, using genetic variants as instrumental variables (IVs). Since alleles are randomly allocated at conception and are not altered by disease processes or environmental and lifestyle factors, MR minimizes bias from confounding and reverse causation.[7] Single nucleotide polymorphisms (SNPs) are commonly used as IVs,[8] enabling estimation of causal effects through their associations with both exposures and outcomes.

MR relies on three core assumptions: (1) Relevance — IVs must be strongly associated with the exposure; (2) Independence — IVs must be independent of confounders of the exposure-outcome relationship; and (3) Exclusion restriction — IVs affect the outcome only through the exposure.[9,10] (Figure 1) These assumptions ensure that MR can robustly estimate causal effects for modifiable risk factors and address limitations of traditional observational studies. Over the past two decades, MR has evolved from its initial use in identifying disease risk factors to broader applications, including elucidating drug mechanisms.[11]

To address different research needs, several MR extensions have been developed: Single-sample MR, the traditional form, estimates causal effects using genetic, exposure, and outcome data from the same cohort via two-stage least squares (2SLS) regression.[12] However, it requires large sample sizes, which may not always be available.[13] Two-sample MR addresses this limitation by using separate GWAS summary statistics for the exposure and outcome from independent samples, with SNPs serving as the link between them.[14] This increases statistical power but requires careful matching of populations to avoid bias from population stratification.[15]

Bidirectional MR helps infer causal direction when genetic variants may influence both variables, making it difficult to disentangle cause and effect. It uses independent IVs for each trait to assess bidirectional relationships.[7] For instance, if A causes B, IVs for A should influence both A and B, while IVs for B should not influence A.

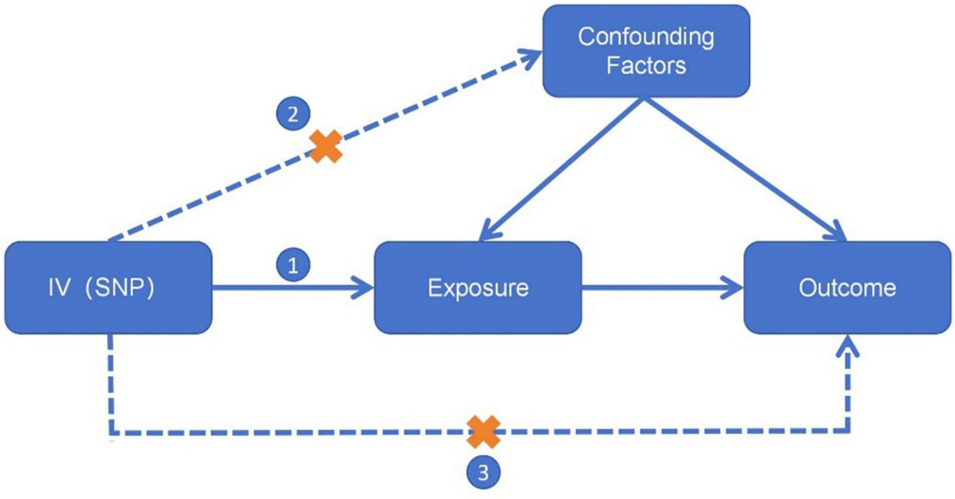

Figure 1 Mendelian randomization core hypothesis diagram.
Notes: The core assumptions of Mendelian randomization include the correlation assumption(①), independence assumption(②), and exclusivity assumption(③). "X" on Path ② indicates that the genetic variant should be independent of all confounding factors. "X" on Path ③ indicates that the genetic variant must influence the outcome only indirectly through the exposure, and not through any direct pathway.
Abbreviations IV, instrumental variable; SNP, single nucleotide polymorphism.

Multivariable MR (MVMR) allows simultaneous evaluation of multiple exposures and their direct effects on an outcome.[16] It requires a sufficient number of independent SNPs and adherence to additional assumptions to account for horizontal pleiotropy and confounding. Mediation MR (MMR) extends MR to decompose total effects into direct and indirect effects mediated through an intermediate variable,[16] providing insights into causal pathways and potential intervention targets when direct modification of the exposure is difficult.

Time-varying MR (TVMR) is an emerging approach that examines how causal effects of exposures on outcomes change over time.[17] It overcomes the limitations of traditional MR, which estimates lifetime average effects, and helps identify critical intervention windows. However, TVMR faces challenges such as age-dependent genetic effects and increased susceptibility to confounding in intergenerational studies.

The MR analytical process typically includes defining datasets, selecting IVs, testing IV assumptions, conducting MR analyses, and performing sensitivity analyses with visualizations.[18] The availability of large GWAS resources, such as the UK Biobank and GWAS Catalog, has greatly enhanced MR research. Common analytical methods include inverse-variance weighted (IVW) estimation and Wald ratio, supplemented with sensitivity analyses such as MR-Egger regression,[19] funnel plots, and Q-statistics to detect and correct for pleiotropy.[20] Combining allele-score and mode-based approaches further improves causal inference accuracy.

Current Research Status of Mendelian Randomization in the Field of Obesity

Exploring the Biological Mechanisms of Obesity Etiology Using Mendelian Randomization

From 2014 to 2024, over 20 studies have systematically revealed multiple influencing factors of obesity through Mendelian randomization methods. As early as 2014, when Mendelian randomization had not yet been widely applied, researchers used MR to find that fetal protein-A from the liver increased the probability of obesity.[21] In 2015, Helle et al demonstrated that the lactase persistence gene leads to obesity by increasing milk intake, although it does not directly cause obesity.[22] Subsequent studies, however, proved that lactase persistence is positively correlated with obesity, suggesting that increasing milk intake in the target population may lead to obesity;[23] thus, the specific impact of the lactase persistence gene on obesity requires further research. In 2017, studies from both China and abroad indicated that the methylation level of the ATP4A gene and DNA methylation at certain gene loci in blood cells may affect BMI.[24] Additionally, Böckerman's research showed that individuals with higher education levels have a significantly reduced likelihood of obesity.[25] In 2018, Tao's study indicated that larger maternal hip circumference is associated with heavier birth weights in infants, emphasizing the importance of preventing excessive maternal weight.[26] In 2019, Mulugeta found that severe depression can lead to obesity through variations in the MC4R gene,[27] and subsequent research indicated that severe depression can also trigger obesity by activating the HPA axis. In the same year, Fu discovered that elevated homocysteine levels increase the risk of obesity,[28] expanding the application scope of MR research. This suggests that MR can be used not only to study influencing factors but also to include any gene-determined substances such as proteins and metabolites in MR research.

Since 2021, there has been an explosive growth in research literature utilizing Mendelian Randomization (MR) to explore the mechanisms of obesity. Dennis's study indicates that a high-fat, low-carbohydrate diet may increase the risk of obesity by 29%,[29] while a 2023 article suggests that an increase in noodle intake can lead to the same result.[30] Research by Shaza and Pang Yao identifies eight proteins that may influence obesity levels: ITIH3, LRP11, SCAMP3, NUDT5, OGN, EFEMP1, TXNDC15, and PRDX6.[31,32] Qian Xu et al revealed a bidirectional causal relationship between gut microbiota (such as Akkermansia and Bifidobacterium) and obesity,[33] with subsequent studies indicating that these may contribute to obesity through metabolites and inflammatory factors.[34] A study focused on children showed that Akkermansia has a protective effect against childhood obesity,[35] suggesting that its impact mechanisms may differ across age groups and warrant further investigation. In 2022, Loukas et al found that the intake of DHA and Omega-3 can reduce the risk of obesity.[36] Yuqian Li demonstrated that the methylation of the SOCS3 gene is associated with obesity.[37] Yuefeng Yu explored the relationship between sleep and visceral fat using both linear and nonlinear MR,[38] and the following year, Yannis used the same method to study the effects of sleep on metabolic syndrome.[39] Bryony also investigated the relationship between sleep and obesity characteristics, with their findings indicating that insufficient

sleep can lead to the accumulation of visceral fat (VAT), promoting obesity, particularly central obesity.[40] Kim et al studied the relationship between smoking and obesity-related characteristics,[41] and the following year, Germán similarly researched this relationship.[42] Unsurprisingly, their results indicated that smoking can lead to an increase in visceral fat, thereby causing obesity. Stefan identified causal associations between the DBNDD1 and ERAP1 genes and obesity.[43] Wang and Li found that specific metabolites in plasma (such as arachidonic acid, arginine, and glycine) and peripheral cells (such as platelets and CD14+ monocytes) are significantly associated with obesity.[34,44] Overall, the Mendelian Randomization method in obesity research has gradually evolved from single-variable studies to multi-sample, multi-variable, and comprehensive factor analyses, encompassing genetic, metabolic, dietary, behavioral, gut microbiota, and socioeconomic dimensions, leading to a more comprehensive understanding of the complex etiology of obesity (Table 1).

Table 1 Summary of Exploring the Biological Mechanisms of Obesity Using Mendelian Randomization

Category	Representative Factors or Markers
Genetics	Lactase persistence gene DBNDD1 gene ERAP1 gene Methylation level of ATP4A gene DNA methylation of certain gene loci in blood cells Methylation of SOCS3 gene
Metabolism	Fetal protein-A Proteins: ITIH3, LRP11, SCAMP3, NUDT5, OGN, EFEMP1, TXNDC15, and PRDX6 Homocysteine Arachidonic acid, arginine, glycine DHA Omega-3 Platelets, CD14+ monocytes
Gut microbiota	Akkermansia Bifidobacterium
Diet	High-fat low-carbohydrate diet Noodle intake
Behavior	Higher education Mother's hip circumference Severe depression Sleep duration Smoking

Abbreviations: BMI, body mass index; WHO, World Health Organization; MR, Mendelian randomization; GWAS, genome-wide association studies; IV, instrumental variable; SNP, single nucleotide polymorphism; MVMR, multivariable Mendelian randomization; TVMR, time-series Mendelian randomization; IVW, inverse variance weighting; VAT, visceral adipose tissue; WHR, waist-to-hip ratio; CAD, coronary artery disease; CVD, cardiovascular disease; AF, atrial fibrillation; PAD, peripheral artery disease; VTE, venous thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; T1D, type 1 diabetes; T2D, type 2 diabetes; LADA, latent autoimmune diabetes in adults; DR, diabetic retinopathy; HDP, hypertensive disorders in pregnancy; PLC, primary liver cancer; NSCLC, non-small cell lung cancer; HL, Hodgkin lymphoma; GMV, gray matter volume; ADHD, attention deficit hyperactivity disorder; HPG, hypothalamic-pituitary-gonadal; PCOS, polycystic ovary syndrome; BioT, bioavailable testosterone; HPA, hypothalamic-pituitary-adrenal; BFR, body fat rate; EAC, esophageal adenocarcinoma; BE, Barrett's esophagus; CRC, colorectal cancer; HGSC, high-grade serous ovarian cancer; FEV1/FVC, forced expiratory volume in one second/forced vital capacity; FEF25–75%, forced expiratory flow between 25% and 75% of vital capacity; IgA, immunoglobulin A. IPF, Idiopathic pulmonary fibrosis; HTN, Hypertension; GH, Gestational Hypertension; CKD, Chronic Kidney Disease; TMD, Temporomandibular Disorder; AD, Alzheimer's Disease; ASD, Autism Spectrum Disorder; SCZ, Schizophrenia; IHD, Ischemic Heart Disease; BC, Breast Cancer; PC, Prostate Cancer; HMB, Heavy Menstrual Bleeding; EC, Endometrial Cancer; BPH, Benign Prostatic Hyperplasia.

Investigating the causal relationship between obesity and its related diseases through Mendelian randomization

Cardiovascular Diseases

Over the past decade, Mendelian randomization (MR) studies have systematically elucidated the causal relationship between obesity and cardiovascular diseases (CVD). Early research focused on key genetic variants such as FTO, MC4R, and TMEM18, demonstrating that elevated body mass index (BMI) significantly increases the risk of heart failure, ischemic stroke, and deep vein thrombosis (DVT). For instance, Sara et al employed a genetic risk score approach and found that each one-unit increase in BMI markedly raised the risk of heart failure.[45] Subsequently, Klovaite and Anette's team identified specific variants (FTO rs9939609, MC4R rs17782313, GNPDA2 rs10938397, BDNF rs10767664) that contribute to ischemic heart disease by modulating lipid metabolism and blood pressure.[46,47] Since 2016, increasing attention has been directed toward the impact of obesity on hemodynamics and coagulation pathways, revealing strong associations with peripheral artery disease and venous thromboembolism (VTE).[48,49] Yuan et al further highlighted that central obesity exerts a greater influence on VTE risk compared to overall obesity.[50] Moreover, Susanna and Benjamin's teams proposed that inflammatory pathways may serve as key mediators linking obesity to aortic valve stenosis.[51,52]

Post-2020, MR studies have adopted more refined approaches, investigating the impact of obesity on microvascular function and incorporating early-life factors. Francesco et al reported that variants in FTO (rs9939609), MC4R (rs17782313), and GNPDA2 (rs10938397) are associated with elevated urinary albumin-to-creatinine ratios, indicating microvascular damage.[53] Research from 2021 suggested that childhood obesity-induced gene expression changes (eg, ADCY3 rs4077678) can have long-lasting effects on the risk of atrial fibrillation, stroke, and atherosclerosis in adulthood.[54–56] Recent studies from 2023 to 2024 have further validated the role of these obesity-associated genes in post-stroke sequelae and heart failure, underscoring the importance of early prevention and intervention.[57–60]

Collectively, MR studies consistently demonstrate that obesity increases the risk of various cardiovascular diseases through multiple pathways, including alterations in metabolism, blood pressure regulation, lipid profiles, and inflammatory responses. BMI-related genes such as FTO, MC4R, and GNPDA2 play central roles in these processes. These advances provide a robust genetic foundation for understanding cardiovascular pathology and support obesity prevention as a key strategy in cardiovascular disease management.

Metabolic Diseases

Obesity exerts significant effects on a wide range of metabolic diseases through multiple biological pathways. As early as 2017, Censin et al demonstrated that genetic variants associated with childhood obesity and insulin sensitivity—including FTO (rs1421085), MC4R (rs6567160), GNPDA2 (rs13130484), ADCY3 (rs11676272), TMEM18 (rs4854349), and SEC16B (rs543874)—increase the risk of type 1 diabetes.[61] Subsequent studies expanded to other common metabolic diseases, such as gout, hypertension, and type 2 diabetes (T2D). For example, Susanna et al reported that obesity-related variants (FTO rs9939609, among others) may contribute to gout by promoting fat accumulation and dysregulating uric acid metabolism.[62] Lee et al confirmed a significant causal relationship between BMI-associated genetic variants and the development of hypertension.[63] Moreover, studies by Tao and Tom et al revealed that these genetic variants not only directly increase the risk of T2D but may also indirectly contribute to coronary heart disease.[64,65]

Since 2023, research has increasingly focused on integrating mechanistic insights. Yuan et al identified that variants in FTO (rs9941349), TMEM18 (rs4854344), BDNF (rs571312), GNPDA2 (rs6752378), and SEC16B (rs7138803) significantly increase T2D risk by influencing lipid metabolism, chronic inflammation, and insulin resistance.[66] In addition, these pathways appear to contribute to diabetic complications such as diabetic retinopathy and gestational hypertension.[67] The long-term impact of childhood obesity has also been repeatedly validated; recent studies suggest that childhood obesity may increase the risk of preeclampsia in adult women via sex hormone regulatory pathways.

MR studies clearly demonstrate that multiple BMI-associated genetic variants systematically increase the risk of metabolic diseases—including diabetes, hypertension, and gout—through mechanisms involving metabolic dysregulation, inflammation, and hormonal imbalances. These findings further highlight the critical importance of early-life interventions to prevent the long-term metabolic consequences of obesity.

Cancer

Since the first report in 2009 linking FTO gene variant (rs9939609) to lung cancer risk,[68] the relationship between obesity and cancer has been progressively elucidated. Early studies focused on variants in FTO, MC4R, and GNPDA2, which were associated with elevated risks of lung cancer, esophageal adenocarcinoma, and colorectal cancer. Aaron et al demonstrated that obesity-related gene variants promote gastrointestinal cancers by influencing gastroesophageal reflux, inflammatory pathways, and gut microbiota, with a more pronounced effect of elevated BMI on colorectal cancer risk in women.[69,70] Caroline et al further revealed sex-specific mechanisms underlying the association between obesity and colorectal cancer.[71] Similarly, Suzanne et al reported that these variants also increase the risk of non-high-grade serous ovarian cancer (non-HGSC).[72]

Since 2021, research has expanded to both hormone-related and non-hormone-related cancers. Muktar's team showed that obesity-associated variants promote risks of multiple myeloma and endometrial cancer through insulin resistance and inflammation pathways, whereas in certain contexts (eg, breast cancer), altered estrogen signaling may confer a protective effect.[73] Mathew et al confirmed the involvement of these obesity-driven pathways in gastrointestinal cancers.[74] In 2022, Wu et al identified associations of FTO (rs9941349), BDNF (rs571312), and GNPDA2 (rs6752378) variants with pancreatic cancer risk, potentially mediated by obesity-induced CRP-driven inflammatory pathways. Abao's 2023 findings further highlighted that variants in AKT1 (rs2498804), IL-6 (rs1800795), and TNF (rs1800629) may regulate PI3K-AKT and JAK/STAT3 signaling in obesity-induced gastric cancer progression.[75]

Recent studies have also emphasized the differential impact of fat distribution on cancer risk. Bai et al reported that body fat percentage is a better predictor of non-small cell lung cancer than BMI,[76] while Xu et al found that visceral and hepatic fat are stronger predictors of primary liver cancer than general obesity. Moreover, in certain cancers, obesity-related variants may exert protective effects. Wu et al demonstrated that HOXC4/5/6 (rs10876528), TBX15 (rs1106529), and GDF5 (rs224333)—which regulate fat metabolism and immune responses—may lower Hodgkin lymphoma risk.[77] Hasnat et al found that in premenopausal women, these variants may reduce breast cancer risk through hormone-regulation pathways;[78] however, other studies reported that obesity significantly increases postmenopausal breast cancer risk,[79] underscoring a menopausal status-dependent effect.

A large body of MR evidence now supports a causal relationship between obesity and multiple cancers. Mechanistically, this involves dysregulated lipid metabolism, inflammatory activation, hormonal axis alterations, and gut microbiota changes. The impact of obesity varies by cancer type, organ specificity, and individual characteristics, suggesting that cancer prevention strategies should account for sex, fat distribution, and physiological stage to enable more precise, subtype-specific interventions.

Psychiatric Disorders

Obesity is intricately linked to various psychiatric disorders through complex genetic and metabolic pathways. Early studies indicated that obesity-related genes may influence brain structure and function. Stéphanie et al reported that the VEGFA (rs6905288) variant may impair angiogenesis and cerebral blood flow, leading to reduced gray matter volume in individuals with abdominal obesity.[80] Additionally, Maria et al found that variants in FTO (rs9939609), MC4R (rs17782313), BDNF (rs10767664), and GNPDA2 (rs10938397) may increase depression risk by altering fat metabolism and inflammatory pathways.[81] Since 2021, research has expanded to include neurodegenerative diseases such as dementia and Alzheimer's disease. Anwar et al reported that obesity may accelerate brain aging,[82] while Zhuang et al identified that specific genes such as CARTPT promote the progression from obesity to Alzheimer's disease.[83]

Emerging evidence also highlights the significant impact of obesity on child mental health. Ding et al revealed that several genes involved in neurodevelopment, metabolism, and synaptic plasticity—DCC (rs11663824), NEGR1 (rs2815752), NCAM1 (rs7106434), INO80E (rs6556833)—may mediate the risk of attention-deficit/hyperactivity disorder (ADHD), depression, and autism spectrum disorders.[84] Amanda and Thais et al further confirmed that these risks are more pronounced among children with higher BMI.[85,86] More recently, in 2023, Chen et al demonstrated that obesity-related variants such as POMC (rs713586) may increase the risk of schizophrenia by modulating energy metabolism and neurotransmitter systems,[87] providing deeper insights into the biological connections between obesity and severe psychiatric disorders.

Overall, obesity increases the risk of various psychiatric disorders through mechanisms involving brain metabolism, inflammation, and neurodevelopmental pathways. The long-term negative impact of childhood obesity on future mental health underscores the importance of early intervention and personalized prevention strategies for psychiatric disorders.

Respiratory Diseases

Between 2019 and 2024, Mendelian randomization (MR) studies have progressively revealed strong causal links between obesity and a variety of respiratory diseases. In 2019, variants in FTO (rs9939609), MC4R (rs17782313), and BDNF (rs10767664) were found to increase asthma risk through pathways involving lipid metabolism and inflammation.[88] Subsequent studies further explored airway structure and immune regulation, identifying variants in ERBB3 (rs4759229), COL16A1 (rs6681149), UNC13D (rs111365807), SMAD3 (rs79071878), and FOXA3 (rs8103278) as contributors to airway remodeling processes, particularly in non-allergic adult asthma.[89–91]

Obesity has also been shown to adversely affect lung function. Nicole et al demonstrated that obesity-related genes impair lung function through inflammatory, metabolic, and neuroregulatory mechanisms, leading to airway obstruction (eg, reduced FEV_1/FVC ratio) and small airway damage (eg, reduced $FEF_{25–75}$%).[92] In children, obesity-related systemic inflammation—mediated by factors such as IL-6 and adiponectin—has also been linked to an increased risk of asthma.[93]

In recent years, research has expanded to other respiratory diseases. Feng et al reported that obesity-related variants (FTO, GCKR, GNPDA2) are associated with chronic obstructive pulmonary disease (COPD), pneumonia, pulmonary embolism, and idiopathic pulmonary fibrosis. Other groups have further shown that these variants, through their effects on BMI, influence the risk of obstructive sleep apnea and acute respiratory distress syndrome (ARDS).

Overall, obesity systematically increases the risk of respiratory diseases via mechanisms involving inflammation, energy metabolism imbalance, and airway remodeling. MR studies provide robust genetic evidence supporting these causal relationships, highlighting the importance of weight control—especially in childhood—for the prevention of chronic respiratory diseases.

Kidney Disease

Although research in this area has emerged more recently, Mendelian randomization (MR) studies have begun to clarify how obesity adversely affects renal health through mechanisms involving metabolic dysregulation, inflammation, and glomerular hyperfiltration. In 2021, Yuan et al reported that variants in FTO (rs9939609), MC4R (rs17782313), SH2B1 (rs7498665), SLC2A9 (rs6449213), and IL-6 (rs1800795) increase the risk of nephrolithiasis via pathways related to energy and uric acid metabolism.[94] Yang et al further demonstrated that these genes are also associated with an elevated risk of chronic kidney disease (CKD), with obesity-related renal damage being particularly pronounced during adulthood.[95] However, Nguyen et al argued that after adjusting for blood pressure and glycemic control, obesity may not be a direct causal factor for CKD.[96] In diabetic nephropathy, Lu et al found that variants in FTO (rs17817449), MC4R (rs6567160), BDNF (rs6265), SEC16B (rs574367), and PAX6 (rs652722) contribute to metabolic abnormalities and inflammatory responses that trigger glomerular hyperfiltration and structural kidney damage, with women showing greater susceptibility.[97]

Recent studies have also explored the link between obesity and immune-related kidney diseases. In 2024, Dong et al reported that obesity may increase the risk of IgA nephropathy through pathways involving sodium channel regulation. Similarly, Zhang et al identified that variants in SCNN1B and SCNN1G mediate the risk trajectory from childhood obesity to diabetic nephropathy in adulthood.[98]

In summary, obesity increases the risk of various renal diseases through pathways involving energy metabolism abnormalities, inflammation, and elevated glomerular pressure. The long-term impact of childhood obesity on renal health should not be underestimated, and effective weight management remains a key strategy for kidney disease prevention.

Reproductive Health

Mendelian randomization (MR) studies have clarified that multiple BMI-associated genetic variants influence reproductive health through mechanisms involving metabolic dysregulation, hormonal imbalance, and abnormal fat distribution. In 2019, Brower et al identified that variants in FTO (rs1421085), MC4R (rs6567160), SEC16B (rs543874), GNPDA2

(rs10938397), PCSK1 (rs261967), BDNF (rs7103411), and MAP2K5 (rs2241420) may increase the risk of polycystic ovary syndrome (PCOS) via insulin resistance and hormonal pathways.[99] Subsequent studies revealed that central obesity has a stronger association with PCOS,[100] maintaining a BMI between 20–25 kg/m² supports normal reproductive function,[101] and variants such as GIPR (rs11672660) and PROX1 (rs3767846) may further mediate the adverse effects of childhood and adult obesity on PCOS risk.[102] In 2022, Samvida et al reported that ZNF664 (rs11057429) is associated with other female reproductive abnormalities, including menorrhagia and preeclampsia.[103] Pubertal development disorders have also gained attention. In 2024, Fang et al found that variants in LIN28B (rs7759938), MKRN3 (rs530324838), and DLK1 (rs1802710) may influence the timing of puberty onset in females by modulating the hypothalamic-pituitary-gonadal (HPG) axis. Zhou et al further demonstrated that INSR (rs1051690) increases endometrial cancer risk through enhanced estrogen exposure and insulin resistance.

In men, studies by Rao and Wan et al showed that variants in FTO (rs1421085), MC4R (rs6567160), SHBG (rs6258), LEPR (rs1137101), CYP19A1 (rs2470152), and IRS1 (rs2943650) affect energy metabolism, sex hormone conversion, and sperm quality, thereby increasing the risk of benign prostatic hyperplasia and infertility.[104,105]

Collectively, these findings suggest that obesity systematically disrupts both male and female reproductive health through multiple pathways, affecting processes from pubertal development and endocrine balance to reproductive system disorders and reproductive cancers. These insights underscore the critical role of obesity prevention and management in safeguarding reproductive health.

Bone and Joint Health

In recent years, researchers have increasingly applied Mendelian randomization (MR) to investigate the impact of obesity on bone and joint health. Early work by Kalliope et al demonstrated that variants in *FTO* (rs8044769), *MC4R* (rs6567160), *LEPR* (rs1137101), and *INSR* (rs1051690) significantly increase the risk of osteoarthritis through pathways involving BMI regulation and inflammation.[106] Subsequent studies highlighted the role of visceral fat in contributing to cartilage wear and joint loading. In 2021, Zhou et al reported that related genetic variants also increase the risk of intervertebral disc degeneration and lumbar spondylosis, potentially via mechanisms involving cartilage metabolism disruption and chronic inflammation.[107]

The long-term impact of childhood obesity has also been explored. Cao et al found that early-life obesity increases the risk of adult knee and hip joint degeneration through fat accumulation pathways.[108] Since 2023, research has expanded into bone density regulation. Victoria's team identified that variants in *SPO3* (rs13204965, rs13194508), *IQCH* (rs3743347), *HOXC4* (rs894738), and *HOXC5* (rs4759320) may reduce bone density through Wnt signaling and bone formation pathways.[109]

Recent studies further clarified the dualistic nature of obesity's effects on bone density. He et al proposed that while increased BMI enhances bone loading and formation, fat-induced inflammation may stimulate osteoclast activity, thereby exacerbating osteoporosis. Ying et al confirmed that childhood obesity elevates long-term osteoporosis risk via metabolic alterations.[110] Additionally, Chen et al observed that in individuals with low BMI, variants related to fat metabolism and cartilage formation increase the risk of temporomandibular joint disorders (TMJD).[111]

Collectively, MR studies reveal a bidirectional effect of obesity on bone and joint health: increased body weight may enhance bone density, but adipose tissue-driven chronic inflammation and metabolic dysfunction can promote osteoporosis and joint degeneration. These insights underscore the importance of optimizing body composition and fat distribution for maintaining bone health.

Skin Diseases

Obesity has been causally linked to a variety of skin diseases, with Mendelian randomization (MR) studies providing strong genetic support for these associations. In 2017, Milena et al identified that variants in *FTO* (rs1558902), *KCNK3* (rs11126666), *POC5* (rs2112347), *GRP* (rs7243357), and *ERBB4* (rs7599312) may elevate the risk of multiple sclerosis through neuroinflammatory and immune regulatory pathways.[112] Notably, the long-term impact of childhood obesity on this disease is particularly pronounced and may involve disruptions in vitamin D metabolism.[113]

Subsequent research has focused on more common skin conditions. Ashley et al reported that variants in *MC4R* (rs7138803), *LEPR* (rs1137101), and *IL-6R* (rs2228145) significantly increase the risk of psoriasis through activation of inflammatory signaling, with higher susceptibility observed in individuals with childhood obesity.[114] In 2020, Yik et al further demonstrated that the *TNF* (rs1800629) variant promotes the development of atopic dermatitis.[115] More recently, in 2024, Huang et al found that obesity may indirectly increase the risk of pressure ulcers by inducing type 2 diabetes, suggesting a potential link between obesity and impaired skin barrier function.[116]

Overall, obesity increases the risk of various skin diseases through mechanisms involving chronic inflammation, metabolic dysregulation, and immune system imbalance. MR studies have been instrumental in elucidating these causal pathways, underscoring the importance of weight management in the prevention of skin-related disorders.

Discussion

In recent years, Mendelian randomization (MR) studies have provided substantial causal evidence, further deepening our understanding of the mechanisms underlying obesity. Initially, MR studies focused on the effects of single genes; however, with the diversification of analytical strategies and expansion of data sources, MR has now widely integrated proteomic, metabolomic, behavioral, dietary, and gut microbiome data. This enables the development of multivariable models to assess the systemic impact of obesity. MR has been extensively applied to investigate causal relationships between obesity and various diseases, including cardiovascular disease, metabolic disorders, and cancer, with a marked increase in publications since 2021 (Figure 2). Findings indicate that the pathogenic effects of obesity vary by age, sex, and physiological status. These studies confirm that the development of obesity and its related diseases involves complex polygenic regulatory networks and multiple signaling pathways across physiological systems such as energy balance, neuroendocrine regulation, glucose metabolism, lipid metabolism, inflammatory response, and immune modulation.

Key polymorphisms and aberrant expression of certain genes serve as the molecular basis for imbalances in energy intake and expenditure, insulin signaling impairment, and abnormal lipid accumulation. Neuroendocrine pathways regulating appetite and energy balance play a central role in obesity susceptibility. MC4R, located in the hypothalamic paraventricular nucleus, suppresses appetite and promotes energy expenditure via α-MSH-mediated activation of the G_s protein and cAMP/PKA signaling pathway.[117] LEPR mediates leptin signaling, activating the JAK2/STAT3 pathway, inhibiting orexigenic NPY/AgRP neurons, and activating anorexigenic POMC/α-MSH neurons, thereby enhancing MC4R-mediated anorexic effects.[118] The BDNF/NTRK2 pathway, via PI3K/Akt and MAPK/ERK signaling, mediates satiety and modulates reward responses, linking obesity to emotional disorders.[119]

In terms of insulin and glucose metabolism, genes such as GIPR, FGF21, and PPARGC1A regulate insulin sensitivity and hepatic glucose-lipid homeostasis. GIPR activation enhances insulin responsiveness in adipose tissue and improves systemic insulin sensitivity.[120] FGF21, through binding to FGFR1c/β-Klotho, activates ERK1/2 signaling to promote glucose uptake in adipose tissue and modulate gluconeogenesis and lipid metabolism in the liver.[121] PPARGC1A regulates mitochondrial biogenesis and oxidative phosphorylation, enhancing metabolic efficiency in skeletal muscle and liver.[122]

Regarding lipid metabolism and adipogenesis, FTO regulates mRNA demethylation and influences preadipocyte differentiation, with high expression associated with adipose tissue expansion.[123] Insulin-induced activation of SREBF1 promotes fatty acid and triglyceride synthesis, exacerbating fat accumulation.[124] ACACB downregulation impairs β-oxidation of fatty acids, enhancing fat storage. The CREBRF variant is strongly linked to obesity in Polynesian populations, highlighting inter-population differences in energy storage regulation.[125]

Chronic low-grade inflammation is another critical mechanism in obesity-related metabolic dysregulation. TNF-α activates NF-κB and MAPK pathways, inducing expression of IL-6 and other cytokines, thereby inhibiting IRS1 activity and promoting insulin resistance.[126] IL-6 also induces CRP expression in the liver via JAK/STAT3 signaling.[127] Additionally, TLR4 activation in obesity triggers macrophage infiltration in adipose tissue, amplifying local inflammation and exacerbating insulin resistance.[128]

Notably, genes such as TRAPPC9, BCL2A1, and TNNI3K, although not traditionally classified within metabolic pathways, indirectly influence obesity-related organ damage by modulating NF-κB activation, apoptosis inhibition, and

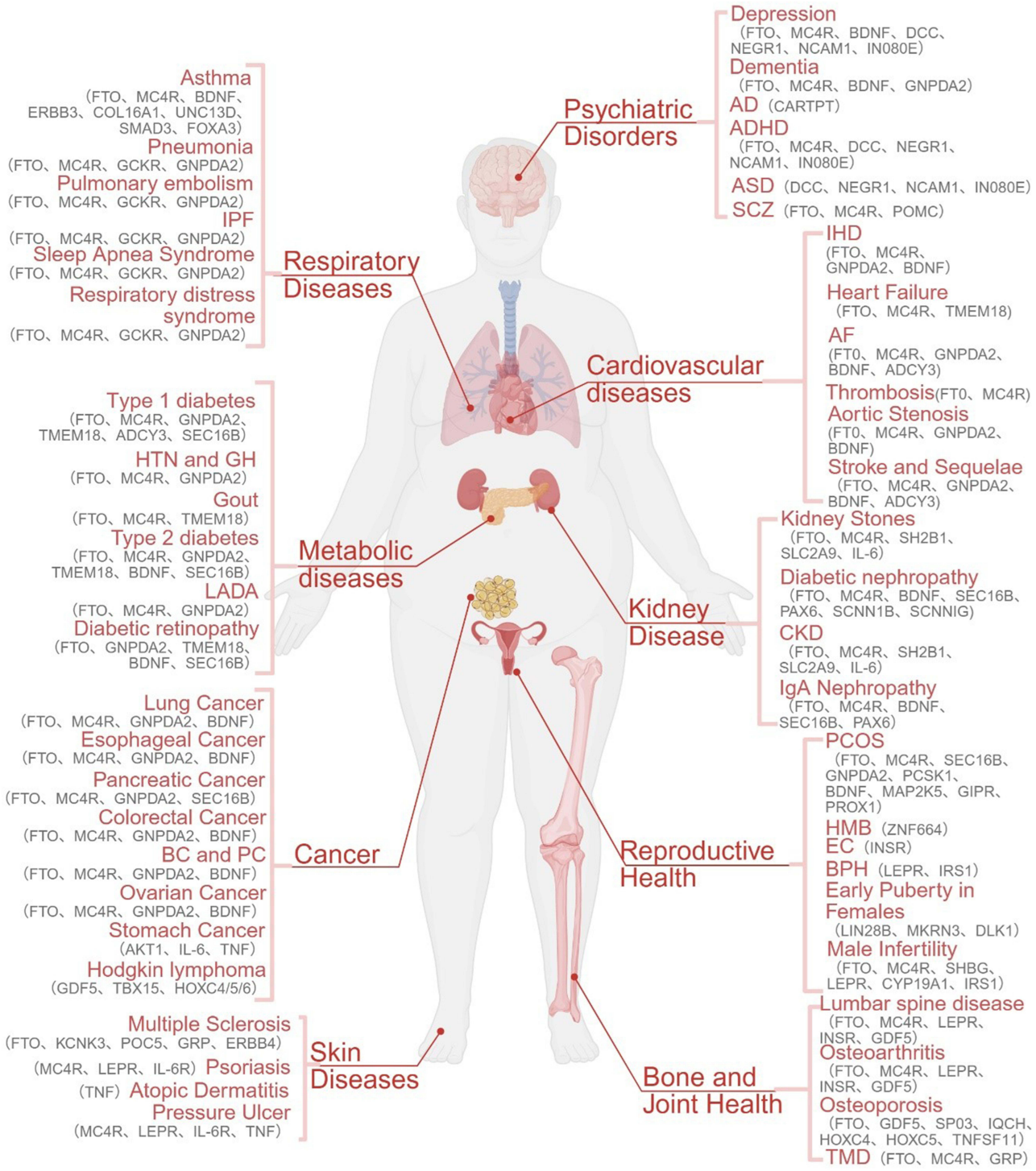

Figure 2 A summary chart of the relationship between obesity and various diseases through genetics.
Notes: Created in BioRender. Shen, A. (2025) https://BioRender.com/gja148q.
Abbreviations: IPF, Idiopathic pulmonary fibrosis; HTN, Hypertension; GH, Gestational Hypertension; LADA, Latent Autoimmune Diabetes in Adults; CKD, Chronic Kidney Disease; IgA, immunoglobulin A; TMD, Temporomandibular Disorder; AD, Alzheimer's Disease; ADHD, Attention Deficit Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SCZ, Schizophrenia; IHD, Ischemic Heart Disease; AF, Atrial Fibrillation; BC, Breast Cancer; PC, Prostate Cancer; PCOS, polycystic ovary syndrome; HMB, Heavy Menstrual Bleeding; EC, Endometrial Cancer; BPH, Benign Prostatic Hyperplasia.

cardiac energy metabolism. TRAPPC9 in particular may bridge neurodevelopment and metabolic signaling, offering new avenues for exploring the "neuro-metabolic" axis.

Several obesity-related molecular targets have advanced into clinical application. MC4R agonists, GIPR/GLP-1R dual agonists, and FGF21 analogs represent cutting-edge therapeutic targets. Setmelanotide, an MC4R agonist, is the first approved treatment for congenital POMC or LEPR deficiency-related obesity, significantly reducing appetite and promoting weight loss.[129] Dual GLP-1R/GIPR agonists, such as Tirzepatide, enhance insulin secretion and improve metabolic outcomes and weight management.[130] FGF21 analogs (eg, Pegbelfermin, Efruxifermin) have shown promise in reducing hepatic steatosis and improving metabolic profiles in NAFLD/NASH patients with obesity.[131] ACCβ (ACACB) inhibitors promote fatty acid β-oxidation and contribute to weight loss in NAFLD/NASH, though gastrointestinal side effects remain a concern.[132]

By contrast, targets such as FTO, SREBP-1c, ADCY3, and SH2B1 remain in early-stage development. While FTO inhibitors demonstrate anti-obesity effects in animal models, challenges related to central delivery and off-target toxicity must be addressed.[133] SREBP-1c inhibitors, such as Fatostatin, suppress lipogenesis-related gene expression in vitro, but in vivo selectivity and toxicity require further optimization.[134] Other promising targets, such as Leptin, BDNF, and CREBRF, present substantial drug development challenges. Leptin therapy is limited by central leptin resistance,[135] and BDNF delivery is hindered by poor blood-brain barrier penetration.[136] CREBRF, a transcription factor, lacks suitable binding pockets for small molecules, necessitating RNA-based or protein-protein interaction targeting approaches.[137] Anti-TNF-α and anti-IL-6R therapies improve insulin sensitivity in animal models but carry infection risks and poor long-term tolerability in humans. Despite these challenges, MR continues to provide valuable genetic insights that support target prioritization for obesity therapeutics.

It is important to note that even within the same gene, different genetic variants may affect disease development through distinct biological pathways. Future research should therefore further explore the potential associations between multiple variants within the same gene and various diseases, providing a stronger genetic basis for identifying novel therapeutic targets for obesity and its related comorbidities. Moreover, childhood obesity exerts long-term adverse effects on the risk of multiple adult diseases, emphasizing the need for early intervention during childhood and adolescence. Efforts from both societal and family levels are essential to prevent the long-term health consequences of obesity in adulthood. Additionally, future research should focus on the differential effects of fat distribution and composition on obesity-related outcomes, enabling a more refined understanding of obesity pathophysiology.

Despite the substantial progress made by MR in elucidating causal relationships between obesity and a wide range of diseases, several limitations remain when applying MR to explore the mechanisms of obesity. First, the validity of MR analysis depends critically on several core assumptions and the robustness of methodological design. The strength of instrumental variables (IVs) is a key determinant of the reliability of causal inference. Weak IVs can introduce substantial bias, resulting in estimates regressing toward the null or yielding misleading conclusions. To mitigate this issue, three-sample designs and partially Bayesian-weighted methods have been proposed to improve estimation efficiency and robustness.[138]

Even with sufficiently strong IVs, MR analyses remain susceptible to horizontal pleiotropy, where genetic variants affect the outcome through pathways unrelated to the exposure of interest. The recently developed MR-LDP model incorporates linkage disequilibrium (LD) structure information to better capture pleiotropic effects and enhance adaptability to complex genetic backgrounds.[139] Population stratification is another often underestimated but critical source of bias. In populations with systematic differences in allele frequencies, MR analyses may yield spurious associations even when no true causal relationship exists.[140] To identify and control for this bias, methods such as the negative control outcome approach—introducing outcomes theoretically unaffected by the exposure—have been employed.[141] Moreover, the MR-Twin approach, which compares siblings within the same family, can effectively account for population structure, environmental confounding, and generational effects without relying on external adjustments, offering clear advantages in controlling for population stratification.[142]

Limitations inherent to GWAS data—the foundational data for MR—also affect the generalizability and accuracy of MR inferences. Most GWAS studies are based on European populations, which limits the external validity of results and hampers their generalization to other ethnic groups. Additionally, some GWAS-identified SNPs lack clear biological

functional annotations. If such variants are used as IVs, they may introduce pleiotropic bias, undermining the credibility of causal inferences.[143] Several strategies have been proposed to address these limitations: first, expanding GWAS sample diversity by including multi-ancestry data to enhance the external validity of MR results; second, prioritizing SNPs with known regulatory functions or expression quantitative trait loci (eQTL) evidence to reduce pleiotropy;[143] and third, leveraging family-based data to improve causal inference accuracy and robustness by controlling for confounding factors.[142]

A second major limitation is that MR is inherently restricted to using genetic variants as IVs, making it difficult to directly assess non-genetic factors such as environmental exposures and lifestyle behaviors, thereby limiting its application in fully elucidating the multifactorial etiology of obesity. Finally, obesity is a complex condition involving interactions across the genome, transcriptome, metabolome, and other biological layers. Its effective treatment typically requires multidisciplinary interventions and combined therapeutic strategies; MR alone cannot provide sufficient clinical guidance. Therefore, it is essential to rigorously assess the core assumptions of MR when constructing models and to complement MR analyses with thorough heterogeneity and sensitivity assessments, as well as other research approaches —such as randomized controlled trials and observational studies—to enhance the precision and reliability of causal inferences.

Conclusion

This review summarizes recent advances in the application of Mendelian randomization (MR) in obesity research, highlighting both methodological developments and its role in causal inference across multiple disease domains. By utilizing genetic variants as instrumental variables, MR effectively controls for confounding bias and has elucidated the causal relationships between obesity and various systemic diseases—including cardiovascular, metabolic, and cancer-related conditions. Additionally, MR studies emphasize the modulatory effects of childhood obesity, sex differences, and fat distribution on disease risk. Key biological pathways and genes, such as *MC4R, LEPR, FTO, FGF21*, and *GCKR*, have been identified, providing a genetic foundation and potential therapeutic targets for the treatment of obesity and its complications. Despite ongoing challenges such as instrument selection and pleiotropy, MR remains a vital tool for advancing precision medicine and informing public health interventions. Future integration with multi-omics and interdisciplinary approaches will further deepen our understanding of obesity mechanisms and support more effective intervention strategies.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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