Metal Ions in Life Sciences

Insights from Genomic Research on Obesity and Emerging Targets for Gene Therapy

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Abstract

The discovery of a genome-wide correlation with obesity-related genes has revealed new information about the genetics of obesity. Given the low proportion of obesity heritability explained by available SNPs, it's not shocking that these SNPs aren't scientifically effective as methods for assessing who would acquire obesity. The roles of the majority of loci, the majority of which map to non-coding sequences, will take thorough analysis to determine the responsible gene at each locus, which may not be the closest gene. This mechanistic information, as well as the resulting elucidation of the pathophysiology of obesity, will allow the creation of new therapies, which could be the primary advantage of these genetic discoveries.

Fortunately, a lack of mechanistic information hasn't stopped researchers from using SNPs and genetic risk ratings to shed light on how obesity biology interacts with environmental and lifestyle influences. These findings suggest that an unhealthy lifestyle may amplify the genetic risk of obesity, despite the fact that environmental studies of obesity genes may be distorted by inaccuracies in diet and physical activity measurement. More research is required to confirm this theory and to identify the specific dietary components (such as sugar-sweetened beverages) that interfere with genetic variants. This study could contribute to personalized obesity prevention and care measures in the future (pending confirmation in clinical trials of genetic-risk-guided interventions). Obesity genetics has offered researchers the opportunity to examine causal interactions between obesity and its various possible complications. However, since the majority of the studies discussed above were conducted on people of European ethnicity, more research is required in minority ethnic groups with a high risk of obesity to understand the role of biology, climate, and relationships among these factors in explaining their increased risk.

Introduction

Obesity is becoming more popular all over the world. Nearly 40% of adults worldwide are overweight, with 10% –15% being obese. 1 Obesity is triggered by the association of an at-risk genetic profile with environmental risk factors including physical inactivity, excessive calorie consumption, the intrauterine climate, drugs, social status, and potentially novel factors like inadequate sleep, endocrine disruptors, and the gastrointestinal microbiota. BMI has been reported to have a heritability of 40–70% (proportion of inter-individual heterogeneity due to genetic factors). 2

While genome-wide association studies (GWAS) sparked research into the genetics of widespread obesity, genetic studies in monogenic obesity set the scene, highlighting the leptin–melanocortin pathway as a central regulator of energy intake.

3 MC4R, BDNF, PCSK1, POMC, SH2B1, LEPR, and NTRK2 are among the genes implicated in monogenic obesity and are found in or close loci linked to obesity-related traits by GWAS. 4 The genetic risk of widespread obesity is the product of the interaction of many loci, each of which contributes a small portion of the overall risk. Researchers are looking at these risk genes to learn more about how obesity progresses. One goal is to use what we've learned to improve human health by informing the development of new therapies to prevent and treat obesity.While mechanistic evidence (which is currently mostly unavailable) is needed for this goal, genetic variants for obesity-related traits have been used to provide various insights into the genetics of obesity and its complications, as discussed below.

An overview of obesity-related genome-wide association studies

Hundreds of genes were tested using candidate gene methods prior to 2007, but only a handful were confirmed as genetic risk factors for obesity. Variants in MC4R and BDNF 5, 6 that were later discovered in GWAS are exceptions. 7 and 8 Four studies published in 2007 linked SNPs in the first intron of FTO (fat mass and obesity associated gene) to obesity-related traits: a GWAS for anthropometric traits,9 a GWAS for early-onset extreme obesity,10 a GWAS for type 2 diabetes,11 and a population stratification analysis that discovered FTO by chance. 12 FTO is the highest signal, and it has been found in people of various ancestries. Following that, activities in broader sample sizes and varied cohorts expanded the number of stable loci for BMI to more than 100. A meta-analysis conducted by the Genetic Investigation of ANthropometric Traits consortium (GIANT) identified 97 loci for BMI, 56 of which were novel. BMI is primarily controlled by processes such as hypothalamic regulation of energy consumption, as shown by the expression enrichment of 13 genes near these loci in the CNS. Just 27% of the variation in BMI is clarified by these 97 loci. SNPs are believed to account for about 30% of the variation in BMI, according to simulation studies,14 suggesting that far more SNPs are yet to be found. Index case bias can trigger false positive and false negative correlations with risk factors (e.g., BMI) in large sample sizes, which may explain paradoxical associations like the diabetogenic allele at TCF7L2 being correlated with lower BMI. 15

The results of genome-wide interaction studies (GWAS) are classified into seven groups for ease of presentation: BMI-related (141 loci); body fat (includes GWAS for body fat proportion and body fat mass; 15 loci); birthweight (eight loci); waist-to-hip ratio or waist circumference adjusted for BMI (97 loci); visceral adiposity (includes GWAS for visceral fat and visceral-to-subcutaneous fat; 15 loci); visceral adiposity (includes GWAS for viscer (includes GWAS for extreme childhood and extreme adult obesity; 23 loci). In Europeans, PBRM1 was related to waist-to-hip ratio balanced for BMI, and in East Asians, it was linked to BMI. Low linkage disequilibrium exists between the COBLL1 SNP associated with waist-to-hip ratio corrected for BMI and the COBLL1 SNP associated with BMI in individuals older than 50 years (r2=014 in Europeans in the 1000 Genomes Project).

GWAS on obesity-related traits other than BMI, especially waist-to-hip ratio have been conducted in a number of studies. In a large-scale GWAS meta-analysis, 49 loci for waist-to-hip ratio corrected for BMI were discovered (to focus on fat distribution rather than total fat). 16 In adipose tissue, gene expression enrichment for genes near these loci was found, indicating that fat distribution is primarily regulated in local fat depots. These 49 loci account for 14% of the variation in waist-to-hip ratio across the board (24 percent in women and 8% in men).

Although the bulk of GWAS has been performed in adults, the Early Growth Genetics (EGG) consortium and others have looked at birthweight, BMI, and general obesity in children, as well as early-onset extreme obesity in children. Many of the same loci have been reported in GWAS for childhood BMI and general obesity as in adult GWAS. Birthweight and early-onset acute obesity, on the other hand, are primarily determined by particular loci, though they share certain genetic factors with BMI and general obesity.

Appendix 2 presents a summary of the GWAS loci discovered for obesity-related traits at the genome-wide significance stage (p5 108) 17 for future studies. These loci are classified by trait families in Figure 1. The waist-to-hip ratio loci do not always coincide with the BMI loci, implying that fat distribution is controlled separately from total adiposity. The overlap of the FTO and MC4R loci as loci for multiple adiposity traits shows their core functions. Future studies into the pathways underlying unique loci shared across several traits (e.g., PBRM1) may be especially useful.

Unique approaches, such as consideration of parent-of-origin effects,18 gene-based GWAS,19 SNPs correlated with variation in BMI,20 and use of specialized fine-mapping arrays, have been used to uncover genetic determinants of obesity-related characteristics in addition to traditional GWAS.21, 22, and 23.

Functional characterisation of genetic associations is required.

A genetic variant's function must be determined before it can be used to create new therapies. This entails determining which gene or genes are influenced by alleles at the variant, as well as the process (e.g., enhancer, repressor, or epigenetic alteration) by which the variant's alleles differentially influence speech. The next step is to figure out how the target gene influences the phenotype in question. When naming SNPs present in GWAS, it's standard practice to use the names of the genes closest to them. This can be deceptive, since SNPs can influence phenotypes by altering gene expression at great distances. The following is an excerpt from the FTO story: FTO is a 2-oxoglutarate-dependent nucleic acid demethylase that is found in the body, but is most abundant in the hypothalamic nuclei that regulate energy balance. 24 The findings of a wide body of studies on FTO have been mixed. 24, 25, and 26 FTO-knockout and FTO-overexpressing mice, for example, all exhibit hyperphagia.27, 28 FTO SNPs tend to impair the expression of other genes. These SNPs physically touch the promoter of a distant gene, IRX3, according to chromatin conformation analysis. 29 Research in mesenchymal adipocyte precursors found that the risk allele at the FTO SNP rs1421085 disrupts a binding site for the ARID5B repressor, resulting in increased expression of IRX3 and IRX5, and shifting the fate of these cells from energy-burning beige adipocytes to energy-storing white adipocytes. 30 Other research has indicated that FTO SNPs on IRX3 have obesogenic effects on the brain29 or pancreas. 31 The danger allele at the FTO SNP rs8050136 disrupts binding of the transcriptional activator P110 (an isoform of CUX1), resulting in decreased expression of FTO and RPGRIP1L, and hence diminished leptin signaling, according to studies in neural cells. 32 and 33 The impact of the FTO locus on distant genes can therefore be tissue-specific and differ depending on the tissue's developmental stage. It's unknown if effects in the brain, adipose tissue, and pancreas all lead to obesity or whether one of these tissues is the main influence. Targeting IRX3, IRX5, or RPGRIP1L, or a combination of these genes, could be needed in future efforts to improve obesity therapies (or preventive strategies). Other obesity loci have not yet attained the same degree of molecular resolution as FTO34, although this information will be gained over time. Until genetic discoveries may be used to enhance human health, a thorough understanding of how a locus influences phenotype is needed. Bioinformatics methods are being developed to help select the most promising SNPs and genes for initial practical interrogation for loci that encompass several genes. 36, 35

Obesity gene-environment associations

Because of the variability of research used in meta-results, inability to account for the spread of BMI, and genetic variations having greater effects in groups of individuals with higher BMI, gene by environment association findings are provided with the disclaimer that such analyses are prone to confounding.

37 The methodological problems of gene-environment interaction research have been carefully studied. 38 Despite these obstacles, the findings of multiple studies presented here show that those with the highest genetic predisposition to obesity are more vulnerable to detrimental environments, implying that potentially unhealthy lifestyle causes do not impact the population equally. Environmental effects on genetic interactions can be mediated by epigenetic changes. 38

Interactions between genes and the obesogenic environment

Obesity has grown significantly over the last four decades. Our genes have not evolved over this time period; however, our climate and lifestyle have. If our world has been more obesogenic in recent decades, it begs the question of whether genetically predisposed people are more vulnerable to obesity in this environment. The correlation of a genetic risk score (panel 1) based on 29 BMI SNPs with BMI was greater in magnitude in individuals born more recently than in those born earlier among 8788 adults born between 1900 and 1958. 41 This result is associated with the general environment being more obesogenic than in previous years, which interacts with genetics to magnify the relationship between genetic risk scores and BMI. The correlation of FTO with BMI was higher in later birth cohorts than earlier birth cohorts in the Framingham Heart Report, with an inflection point about 1942. 42 A 32-SNP BMI genetic risk score showed a favorable association by birth year for BMI, waist circumference, and skinfold thickness in about 900 people born between 1901 and 1986. 43 In recent generations, even monogenic conditions like MC4R deficiency seem to have become more penetrant. 44

A GWAS meta-analysis of SNP by age associations found 15 loci (including FTO) with age-modified effects on BMI, 11 of which had a greater effect on BMI in people under 50.

45 Some of these effects are likely due to our increasingly obesogenic climate, while others could be due to a biological impact of aging or an increase in non-genetic control as people get older (ie, accumulating effects of environmental factors). Both options coexist, according to a survey of over 8000 people from the Framingham Heart Study. 46 A randomized analysis of people born over the span of one week revealed that a genetic risk score dependent on 11 SNPs related to adult BMI was linked to weight gain in childhood but not in adulthood. 47 According to a systematic study, the genetic contribution to BMI in children could be greater than in adults. 48

The UK Biobank study (which included up to 120 000 European individuals with a genetic risk score of 69 BMI SNPs) showed that no single environmental cause, out of the 12 studied, was primarily responsible for the increased correlation of genetic risk score with BMI in the obesogenic setting. 37 Physical exercise, sedentary time, TV consumption, and western diets were all observed to interfere with the genetic risk score on BMI.

If modernisation is obesogenic, obesity-related variants should be exacerbated in urban and rural environments. For FTO in South Asians, no evidence of a gene-urban-environment relationship has been recorded. 50, 49 Similarly, a Korean study found that the climate, whether urban or rural, would influence genetic influences on abdominal adiposity. 51

Interactions of genes and smoking

There has been no evidence of a connection between smoking and BMI.

The 52 SNP rs1051730 in the CHRNA5–CHRNA3–CHRNB4 gene cluster, which is closely related to smoking quantity in smokers, was found to be correlated with lower BMI only in smokers, indicating that smoking has a causal effect on BMI reduction.

A novel SNP in the FLJ33534 locus was discovered by 53 GWAS in a Pakistani cohort, and its influence was modified by smoking, with the minor allele correlated with lower BMI in current smokers and higher BMI in never smokers. 54 SNPs near MC4R and POC5 nominally indicated association with smoking on teenage BMI in European Americans, while one SNP near TNNI3K showed a heavy interaction in Hispanic Americans, according to another report. 55 The correlation between BMI and all three SNPs was stronger in smokers. This sounds counterintuitive, considering that smoking is related to a lower BMI and that people who avoid smoking often gain weight. 56 Four SNPs were shown to have nominal associations in a sample of 95 BMI SNPs in about 8000 Pakistani adults, three of which amplified the correlation with BMI in smokers. 57 A large-scale GWAS meta-analysis found 23 new smoking-related associations and nine loci of gene-by-smoking interactions on BMI, waist circumference, and waist-to-hip ratio in a large-scale GWAS meta-analysis. The CHRNA5–CHRNA3–CHRNB4 interaction was repeated, and 58 genes near the novel loci are implicated in addictive activity and oxidative stress. SNPs explained more variation in BMI in smokers than in non-smokers, but less variance in waist-to-hip ratio in non-smokers. In conclusion, smoking has been shown to amplify the correlation of particular BMI-related SNPs with BMI, thus dampening the association of waist-to-hip ratio SNPs with waist-to-hip ratio in many reports. These findings indicate that, although smoking can have an effect on decreasing BMI in general, smoking abstinence may be prescribed for people with the greatest hereditary risk of obesity.

Interactions of genes and alcohol

In the case of alcoholism, the genetic control of BMI can be different.

59 The Glu504Lys (rs671) variant in ALDH2 (mitochondrial) has been related to alcohol aversion in about half of East Asians who lack the enzyme's involvement, resulting in unpleasant symptoms after drinking alcohol. 60 The Lysine allele has been related to a lower intake of alcohol, which is unsurprising. 61 In terms of how the Glu504Lys (rs671) variant interacts with obesity phenotypes, an analysis of 2958 Chinese people showed that the Glu504Lys (rs671) variant was linked to visceral fat only in frequent drinkers, suggesting that lower alcohol intake in Lysine allele carriers may lead to less visceral adiposity. 62 In another study, higher levels of alcohol intake reduced the relationship between FTO and BMI. 52

Interactions between genes and socioeconomic status

The correlation of a 29-SNP genetic risk score with BMI was nominally magnified by persistently low socioeconomic status or downward mobility (decreasing socioeconomic status over time) among approximately 9000 non-Hispanic European individuals, while persistently high socioeconomic status or upward mobility dampened the association.

63 The UK Biobank analysis found comparable findings for social status and genetic risk ranking, with the Townsend deprivation index seeming to better reflect the obesogenic climate. 37

Other associations between genes and the environment

Chronic psychosocial stress can influence adiposity phenotypes by interacting with genetic predisposition.

64 and 65 It was also discovered that increasing the difference between the mean sleep time amplified the relationship between FTO and BMI. 52 In terms of changing the relationship with BMI or adiposity, however, no robust interactions were found between individual GWAS SNPs and completed college education66 or between a 69-SNP genetic risk score and years of education. 37

Obesity gene-by-gene associations

The best-known gene-by-sex associations are some loci that are more intensely (or solely) correlated with waist-related phenotypes in women than in men.

67, 16 A large-scale genome-wide association analysis discovered 44 loci for waist-to-hip ratio (adjusted for BMI) that showed sexual dimorphism, with 28 loci having greater effects in women, five loci having larger effects in males, and 11 loci having opposite effects in men and women. 45 There was no correlation between sex and BMI loci in this research. In comparison, four novel BMI loci were discovered in a major GWAS meta-analysis in people of Asian descent, two of which (KCNQ1 and ALDH2) demonstrated greater correlations in men than in women. 68 Following that, a targeted study of BMI, waist circumference, and waist-to-hip ratio variants in 2958 Chinese people found correlations of MC4R with visceral fat area and LYPLAL1 with subcutaneous fat area in women only, and ALDH2 with visceral fat area in men only. Three loci for BMI and four loci for waist-to-hip ratio demonstrated sexual dimorphism in a 62 GWAS meta-analysis of people with African descent. 69 This findings suggest that gene-by-sex relationships can be influenced by ancestors.

Obesity gene-by-lifestyle connections

Interactions of genes and diet

Sugar-sweetened soda consumption has been linked to weight gain and problems such as diabetes in several trials. Increased intake of sugar-sweetened beverages amplified the association of a 32-SNP genetic risk score with BMI, according to analyses in the Nurses' Health Study (6934 women) and the Health Professionals Follow-up Study (4423 men) with replication in the Women's Genome Health Study (21 740 women), with the genetic effect roughly doubled by comparing the lowest with the highest sugar-sweetened beverage intake. 70 Furthermore, the link between sugar-sweetened soda consumption and BMI was greater in those with higher genetic risk scores than in those with lower genetic risk scores. There was a related association effect between genetic risk score and sugar-sweetened beverage consumption for incident obesity.70 However, no association between a 69-SNP BMI genetic risk score and so-called fizzy drink consumption on BMI was identified in a sample of the UK Biobank, which involved about 46 000 participants. 37

The Nurses' Health Survey, Health Practitioners Follow-up Study, and Women's Genome Research Study cohorts were all used in the same way to prove that the 32-SNP genetic risk score's association with BMI was amplified among those who consumed more fried food.

71 Furthermore, the influence of fried food intake on BMI was greater in people with higher genetic risk scores than in people with lower risk scores. In the UK Biobank, this influence of fried food intake was not observed. 37

A genetic risk score composed of 32 BMI-associated SNPs and a genetic risk score composed of 14 waist-to-hip ratio-associated SNPs were used in a large-scale study for gene and diet (assessed as a composite balanced diet score) association. 72 A substantial genetic risk score by healthy diet score interaction was not observed in this meta-analysis72 for the BMI-associated genetic risk score with BMI, but nominally significant correlations were observed for the waist-to-hip ratio genetic risk score and healthy diet score with waist-to-hip ratio corrected for BMI. In contrast to the previous studies70, 71, which found that unhealthy dietary factors amplified the correlation of genetic risk score with obesity-related characteristics, the meta-analysis72 found that the association of genetic risk score with waist-to-hip ratio was stronger with higher healthy diet scores.Biased self-reporting of diet was suggested by the writers as a potential reason for the unexpected outcome. If future research confirms an increased genetic impact on waist-to-hip ratio in the context of balanced diet conditions, this may indicate that fat distribution (waist-to-hip ratio) is regulated differently by genes than total adiposity (BMI). Major gene by diet signals for individual diet components may have been obscured by the composite balanced diet ranking. Other research that looked at non-specific dietary factors (total energy, sugar, carbohydrate, protein, or fiber) showed no effect of genetic risk score through diet associations on adiposity scales. 73, 37 While some studies on FTO found that higher calorie intake, higher protein intake, higher saturated fat intake,77, 78, and those who add salt to their diet increased its association with BMI,52, a large study (177 300 adults) found no associations between FTO and total energy, protein, carbohydrate, or fat intake and BMI.79

interactions between genes and physical activity

Physical exercise reduced the impact of a 12-SNP genetic risk score on BMI and obesity risk in more than 20 000 people. 80 Physical activity at 36 years dampened the correlation of an 11-SNP genetic risk score with BMI at the same age in 2444 participants, and physical activity at 53 years dampened the association of the genetic risk score with the rate of improvement in BMI from 53 to 63 years in 2444 participants. 81 Physical exercise reduced the connection between a 69-SNP genetic risk score and BMI in over 109 000 people in the UK Biobank. 37 These studies indicate that physical exercise can help people overcome an inherited predisposition to obesity. In all of the findings, people with the highest genetic risk of obesity (higher genetic risk scores) benefited the most from physical exercise, even at low levels of fitness.

A meta-analysis of 111 421 European ancestry individuals discovered a nominally relevant 12-SNP genetic risk score through physical activity interaction on BMI, which was overwhelmingly influenced by individuals from the American cohorts and not seen in the European cohorts82, increasing the likelihood of population-specific interaction results. Physical exercise reduced the genomic impact on BMI in people aged 21 to 50, according to the Framingham Heart Study in the United States. 46 Increased physical activity nominally decreased the correlation of a 28-SNP genetic risk score with BMI in a cohort of 2894 Chinese Han people.83 A 95-SNP genetic risk score, on the other hand, found no correlation between physical activity and BMI among about 8000 Pakistani people. 57 Why a genetic risk score by physical activity interaction exists in American and Chinese populations but not in European or Pakistani populations is unknown. More research is needed to ensure that these variations are not coincidental, given that the relationship has been observed in several European cohorts80.

In the Nurses' Health Research and Health Practitioners Follow-up Study, an analysis of a 32-SNP BMI genetic risk score showed that leisure time spent on physical activity decreased the genetic risk score's correlation with BMI.

84 The correlation of the genetic risk score with BMI was also shown to be exacerbated in the presence of increased sedentary behavior in this study (measured as weekly hours of television watched). The interactions between genetic risk score and physical exercise and sedentary behavior are unrelated. This result implies that physical exercise and sedentary behavior are two separate goals for obesity treatment. Sedentary time and hours spent watching television were separately tested for genetic risk score interaction on BMI in about 120 000 people in the UK Biobank study; sedentary time showed a high interaction, whereas watching television showed a nominal interaction. 37

Several experiments have looked at the association between the FTO locus and physical activity, but the findings have been mixed. A meta-analysis of 218 166 adults and 19 268 children and teenagers is the most convincing study. 85 Only in adults was there an interaction between FTO genotype and physical exercise, with the chances of obesity being 130 per obesogenic allele in the inactive group and 122 per allele in the active group, indicating a 27 percent decrease in risk of physical activity. Physical exercise attenuated the impact of just FTO on baseline and follow-up (median 33 years) BMI and body adiposity index in a prospective multiethnic cohort. 86 Only FTO was shown to have an impact on BMI modified by physical exercise in a genome-wide interaction meta-analysis of 200 452 adults (90 percent European). No interaction effects on waist circumference or waist-to-hip ratio were found. 87

These studies indicate that physical exercise can reduce the impact of bad genes on obesity risk. As a result, those who are more at risk should be properly advised to follow an active lifestyle. Individuals will now discover their vulnerability based on GWAS variants due to direct-to-consumer genetic profiling. However, presenting such information without adequate therapy may have unintended effects. A meta-analysis of genetic risk-based counseling through various situations discovered that knowing about genetic risk had no effect on behavior. 88 In high-risk people, counseling focused on the genetic risk of obesity decreased self-blame and increased incentive to make dietary improvements, but did not result in weight loss. 89, 90, 91, 92, 93, 94, 95, 96 In one study, people who discovered they had a greater genetic chance of obesity increased their fat consumption and did less leisure-time exercise than they had previously. 92 As a result, the same people who stood to benefit the most from a healthier lifestyle reacted negatively after discovering their genetic risk, perhaps believing that they were doomed by their genes. As personalised genomic profiling becomes normal, it is predicted that high-risk persons may escalate rather than de-intensify their lifestyle with adequate therapy. This begs the important question of whether individuals' capacity to shed weight is harmed by detrimental obesity genetics.

Interactions between genes and weight loss interventions

The effect of diet, exercise, or drug intervention on weight loss has been studied to see whether genotype plays a role. This is a distinct gene-by-lifestyle relationship (with weight loss as the result) than the one discussed previously (where the outcome was BMI or obesity). The effect of the FTO genotype on reaction to a weight loss intervention has been controversial in intervention trials (usually with small sample sizes). The FTO genotype has little impact on the reaction of BMI, weight, or waist circumference to diet-, substance-, or exercise-based weight reduction treatments, according to a meta-analysis93 of individual patient-level evidence from eight randomised controlled trials. A 16-SNP genetic susceptibility score has no associations with treatment modality in weight loss or weight regain in the Diabetes Prevention Program94. A 30-SNP genetic risk score was correlated with bodyweight at baseline but not with weight change in a Danish trial95 of intensive lifestyle intervention; no association between genetic risk score and physical exercise on weight change was found. None of the 13 SNPs tested in the Look AHEAD study, which looked at an intensive lifestyle intervention in overweight and obese people with type 2 diabetes, were linked to weight loss at one year, but there was a weight regain association between FTO genotype and treatment community.In a collaborative review of the Diabetes Prevention Program and Look Forward, none of the 91 obesity SNPs are associated with weight loss or regain.97 There was no connection between the SNPs and weight gain during a low-calorie diet in the DIOGENES sample of 651 SNPs in 69 genes, including FTO. 98 Overall, these findings show that BMI SNPs do not affect the effectiveness of lifestyle-based weight loss measures, including aggressive attempts, which is a valuable message for genetic counseling.

The few experiments that have been performed on bariatric surgery have been too limited to offer definitive proof of gene-intervention interactions. The largest interaction analysis to date discovered that one FTO SNP, rs16945088, modulated weight loss after gastric banding but not gastric bypass; this SNP is not in linkage disequilibrium with FTO SNPs reported in GWAS for obesity-related characteristics, and the GWAS-discovered FTO SNPs were not associated with weight loss after surgery. 99 More and larger studies of gene-by-surgery interactions on weight loss are expected.

Obesity genetic variations are being used as testing instruments to determine the cause.

GWAS loci (typically FTO or genetic risk score) have offered valuable instruments to investigate causal correlations between obesity and disorders for which epidemiological research indicates obesity is a risk factor, in addition to elucidating the genetics of obesity itself. Obesity has been attributed to a variety of risks in observational studies; however, correlation does not imply causation. The connection may be due to reverse causation or other (often unmeasured or unknown) causes that affect both obesity and the complications. The risk factor (in this case, obesity) is replaced by genetic loci for that risk factor, which are then analyzed for their ability to predict the result or complication in mendelian randomisation or instrument variable analysis. Since confounding phenotypes or reverse causality have little effect on genetic variants, this study can be used to determine if the risk factor has a causal relationship with the result. The instrument variable must therefore be a reliable representation of the predictor variable for this method to work. Furthermore, the risk factor's genetic variations must not be related to possible confounders or be in linkage disequilibrium with SNPs linked to other risk factors (pleiotropy). It's also up for discussion whether FTO and BMI genetic risk ratings are fairly free of pleiotropy. 100 Mendelian randomization analyses may be skewed by population stratification (chance genetic variations between cases and controls, mostly resulting from unrecognized ancestral differences). Many of the above problems are specifically discussed in the most rigorous mendelian randomization analyses. 102

Formal studies combine epidemiological and genetic data to determine the causal relationship between the risk factor and the result (ie, the effect of genetically increased BMI on the outcome). Less systematic studies look only at the relation between genetic loci for the risk factor and the outcome, or they look at loci that link the risk factor and the outcome (eg, overlapping loci from GWAS for both). This paper focuses on research that looked at mediation between obesity and other characteristics using systematic mendelian randomization analyses. Other models that may refer to obesity loci, such as pleiotropy and moderation, are not addressed. Although not fully convincing, mendelian randomization has proven exceptionally helpful in assessing the cause of obesity with a number of characteristics.

Factors and activities associated with cardiometabolic disease

In this sense, Mendelian randomization studies have typically produced predicted causal correlations between BMI and metabolic traits. For fasting glucose and LDL cholesterol, the evidence for the cause of BMI is mixed. The dominant opinion that obesity causes diabetes by exacerbating insulin resistance is supported by repeated causal correlations of BMI with type 2 diabetes and fasting insulin. Total adiposity (BMI) influences insulin secretion, while fat distribution (waist-to-hip ratio) influences insulin resistance, according to Mendelian randomization and basic correlation studies; 108, 109 changes in both insulin secretion and insulin resistance should result in increased fasting insulin. Obesity may be the root cause of the metabolic syndrome, based on the strong causal correlations of BMI with other components of the syndrome (blood pressure, triglycerides, and HDL cholesterol).

The connection between obesity and a number of cardiovascular risk factors poses the question of whether obesity is directly (via body mass) or indirectly (via other factors) responsible for cardiovascular disease events (eg, given its association with lipids). The majority of evidence confirms BMI as a causal factor in coronary heart disease 110, 111, 112. Coronary heart disease was one of many characteristics examined in two studies 103 and 105 that did not find BMI to be causal for coronary heart disease; additionally, one of the studies103 used only FTO as the instrument predictor, while the other had some suggestion of causality.According to a mediation study, LDL cholesterol, remnant cholesterol, and systolic blood pressure each mediate 7–8% of the impact of obesity on coronary heart disease, with no mediating effect of reduced HDL cholesterol or increased C-reactive protein. 116th For stroke, the data is mixed, but mendelian randomization trials have suggested that obesity causes heart attack, atrial fibrillation, and peripheral arterial disease. Obesity must be studied using genetic risk scores to decide whether it is the source of coronary or all-cause mortality.

Cancer

Obesity has long been thought to play a part in the development of multiple cancers. Breast cancer is one of the few disorders that has an opposite relationship with BMI. With the notable exception of prostate cancer, elevated BMI is the cause of increased cancer risk in the majority of other cancers studied. This body of work helps to firmly establish obesity as a risk factor for several cancers and rules it out for others, providing the basis for mechanistic research into the role of obesity in neoplasia and strong evidence for weight loss as a preventive measure for specific cancer types.

Characteristics and diseases in psychiatry and neuroscience

Obesity's possible causal role in a variety of neuropsychiatric traits and disorders has been investigated using genetics. In some of these states, reverse causality is a big concern; for example, people with depression or schizophrenia can follow weight-gaining lifestyles or taking drugs (e.g., atypical antipsychotics) that encourage weight gain. Obesity has a causal role in multiple sclerosis, but it has been found out in Alzheimer's disease, bipolar disorder, and schizophrenia in mendelian randomization trials. Obesity does not seem to play a causal role in depression, according to current research. The existence of an apparently contradictory impact of increased BMI on decreased psychological distress must be verified. 129

Characteristics and diseases of reproduction

Obesity has an effect on reproductive wellbeing, and mendelian randomization has been used to investigate causality. Obesity and puberty timing can share a genetic origin, according to studies. 132 The average age of menarche has decreased over the last 50 years, most likely as a result of the current obesity crisis.A Mendelian randomisation study of 8156 women found that BMI in infancy was causal for menarche by the age of 12 years. 132 However, a 42-SNP genetic risk score for age of menarche was associated with BMI in 556 children, raising the possibility of bidirectional causality. number is 132.

In polycystic ovary syndrome, the role of obesity as a causal factor versus only as an exacerbating factor has long been debated. Mendelian randomisation analysis of 32 SNPs suggests a causal association of BMI with polycystic ovary syndrome. 132

Such characteristics and circumstances

Although an association between obesity and bone-density-related phenotypes has long been recognised, mendelian randomisation studies of bone phenotypes have been done in relatively small sample sizes and yielded mixed results. Obesity is linked to numerous additional conditions, many of which have been interrogated in mendelian randomisation analyses. In addition to the studies that looked at a variety of tumors, there were also studies that looked at a single cancer. 118, 119, 134 and multiple cardiometabolic phenotypes,103, 106 other studies have used mendelian randomisation to examine the causality of obesity simultaneously for multiple traits (a phenome-wide approach). 135 and 107 Importantly, these studies accounted for multiple testing.

Although epidemiological and genetic correlation has been documented between BMI and sleep-related phenotypes, such as a person's chronotype (morning or evening type), under-sleeping, oversleeping, or excessive daytime sleepiness, large-scale mendelian randomisation analyses have not been able to establish causality. 136, 137, 138 Mendelian randomisation analyses have produced conflicting results on whether obesity is causal of asthma. 139, 140 Obesity appears to be the cause of features of diabetic kidney disease in type 1 diabetes.141

The associations of several biomarkers with BMI have been informatively clarified in bidirectional mendelian randomisation analyses, wherein investigators tested a genetic instrument variable for BMI for causality with the biomarker, and tested a genetic instrument variable for the biomarker for causality with BMI. As chronic low grade inflammation is a risk factor for cardiometabolic disease, these findings clarifying the association between adiposity and markers of inflammation, such as C-reactive protein, are clinically relevant. 142 Nanomedicine applying gene therapy strategies 165-176 have elegant endeavour for treatment of various gene polymorphisms and mutations of complex disorders 177-191.

Conclusion

GWAS for obesity-related traits have provided new insights into the biology of obesity. Given the low proportion of heritability explained by available SNPs for obesity, it is not surprising that these SNPs are not clinically useful as tools to predict who could develop obesity. 39 Although the mechanism of the FTO locus is being described at the molecular level, the functions of the majority of loci, most of which map to non-coding sequences, will require extensive investigation to identify the responsible gene at each locus, which might not be the nearest gene. This mechanistic information, and consequent elucidation of the pathophysiology of obesity, will allow development of new treatments, which could ultimately be the main benefit of these genetic discoveries.

Fortunately, lack of mechanistic knowledge has not prevented the fruitful use of SNPs or genetic risk scores as tools to shed light on the interactions of obesity genetics with environmental and lifestyle factors. Noting that obesity genes by environmental studies might be biased by imprecision in the measurement of diet and physical activity,38 these studies suggest that an adverse lifestyle could amplify the genetic risk of obesity. Further studies are needed to solidify this notion and clarify the particular dietary components (eg, sugar-sweetened beverages) that interact with genetic variants. This research could eventually lead to personalised obesity prevention and treatment measures (pending confirmation in clinical trials of genetic-risk-guided interventions). Obesity genetics has provided the tools to explore causal associations between obesity and its multiple potential complications. However, because most of the studies described above were done in individuals of European ancestry, additional studies are needed in minority ethnic groups that are at high risk of obesity to elucidate the contributions of genetics, the environment, and interactions thereof that might explain their increased risk.

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