Obesity 1

Genetics of obesity: what genetic association studies have taught us about the biology of obesity and its complications

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Genome-wide association studies (GWAS) for BMI, waist-to-hip ratio, and other adiposity traits have identified more than 300 single-nucleotide polymorphisms (SNPs). Although there is reason to hope that these discoveries will eventually lead to new preventive and therapeutic agents for obesity, this will take time because such developments require detailed mechanistic understanding of how an SNP influences phenotype (and this information is largely unavailable). Fortunately, absence of functional information has not prevented GWAS findings from providing insights into the biology of obesity. Genes near loci regulating total body mass are enriched for expression in the CNS, whereas genes for fat distribution are enriched in adipose tissue itself. Gene by environment and lifestyle interaction analyses have revealed that our increasingly obesogenic environment might be amplifying genetic risk for obesity, yet those at highest risk could mitigate this risk by increasing physical activity and possibly by avoiding specific dietary components. GWAS findings have also been used in mendelian randomisation analyses probing the causal association between obesity and its many putative complications. In supporting a causal association of obesity with diabetes, coronary heart disease, specific cancers, and other conditions, these analyses have clinical relevance in identifying which outcomes could be preventable through weight loss interventions.

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This is the first in a Series of three papers about obesity

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Introduction

Obesity has become increasingly common across the globe. Worldwide, nearly 40% of adults are overweight and 10–15% are obese.[1] Obesity arises from the interactions between an at-risk genetic profile and environmental risk factors, such as physical inactivity, excessive caloric intake, the intrauterine environment, medications, socioeconomic status, and possibly novel factors such as insufficient sleep, endocrine disruptors, and the gastrointestinal microbiome. The heritability (proportion of inter-individual variation attributable to genetic factors) of BMI has been estimated to be 40–70%.[2]

Although research into the genetics of common obesity was catalysed by genome-wide association studies (GWAS), the stage was set by genetic studies in monogenic obesity, which highlighted the leptin–melanocortin pathway as a key regulator of energy intake.[3] Several genes implicated in monogenic obesity are in or near loci subsequently associated by GWAS with obesity-related traits, including *MC4R*, *BDNF*, *PCSK1*, *POMC*, *SH2B1*, *LEPR*, and *NTRK2*.[4] The genetic risk of common obesity reflects the accumulation of multiple loci, each contributing a small portion of the total risk. Investigators pursue these susceptibility genes to improve our understanding of why obesity develops. One goal is to use this knowledge to improve human health, by informing the development of new drugs to prevent and treat obesity. Although this goal requires mechanistic information (which is largely unavailable today), genetic variants for obesity-related traits have been exploited to provide numerous insights into the biology of obesity and its complications, as reviewed below.

Overview of genome-wide association studies in common obesity

Before 2007, candidate gene approaches examined hundreds of genes, but few were confirmed as genetic risk factors for obesity. Exceptions include variants in *MC4R* and *BDNF*[5,6] that were later identified in GWAS.[7,8] In 2007, four reports associated SNPs in the first intron of *FTO* (fat mass and obesity associated gene) with obesity-related traits: a GWAS for anthropometric traits,[9] a GWAS for early-onset severe obesity,[10] a GWAS for type 2 diabetes,[11] and a population stratification study that incidentally discovered *FTO*.[12] *FTO* remains the strongest signal and has been detected in multiple ancestries. Subsequent efforts in increasingly larger sample sizes and in cohorts of diverse origin (appendix 1, pp 1–5) have increased the number of robust loci for BMI to more than 100 (figure 1, appendix 2). A Genetic Investigation of ANthropometric Traits consortium (GIANT) meta-analysis (comprising more than 339 000 individuals) identified 97 loci for BMI, 56 of which were novel.[13] Genes near these loci showed expression enrichment in the CNS, suggesting that BMI is mainly regulated by processes such as hypothalamic control of energy intake. These 97 loci explain only 2·7% of the variance in BMI.[13] Simulation studies have suggested that SNPs account for around 30% of variance in BMI,[14] implying that many more SNPs remain to be discovered. In large sample sizes, false positive and false negative associations with risk factors (eg, BMI) can arise from index event bias, possibly explaining paradoxical associations such as the diabetogenic allele at *TCF7L2* being associated with reduced BMI.[15]

Numerous GWAS have focused on obesity-related traits other than BMI, particularly waist-to-hip ratio

See Online for appendix 1

See Online for appendix 2

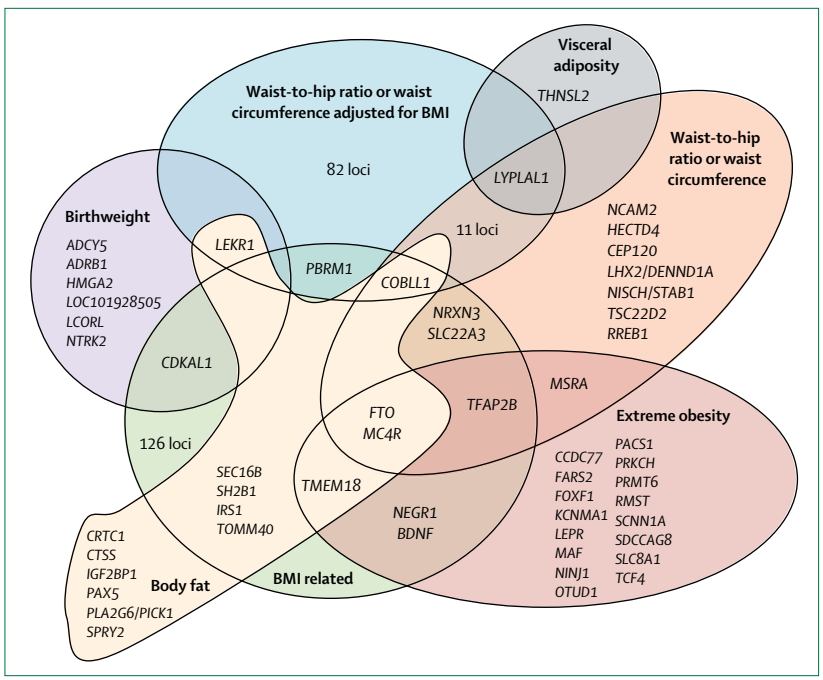

***Figure 1*: Major GWAS discoveries for adiposity traits**

For clarity of presentation, findings of genome-wide association studies (GWAS), shown in appendix 2, are grouped into seven categories: BMI related (includes GWAS for BMI, weight, overweight or obese status in adulthood, childhood BMI, childhood obesity, and BMI change over time; 141 loci); body fat (includes GWAS for body fat percentage 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 adipose tissue ratio; two loci); waist-to-hip ratio or waist circumference (includes GWAS for waist-to-hip ratio and waist circumference not adjusted for BMI; 26 loci); and extreme obesity (includes GWAS for extreme childhood and extreme adult obesity; 23 loci). *PBRM1* was associated with waist-to-hip ratio adjusted for BMI mainly in Europeans and associated with BMI in East Asians. The *COBLL1* SNP associated with waist-to-hip ratio adjusted for BMI and the *COBLL1* SNP associated with BMI in individuals older than 50 years are in low linkage disequilibrium (r^2=0·14 in Europeans in the 1000 Genomes Project). Appendix 2 lists GWAS results for additional categories of adiposity traits not depicted in the figure.

(appendix 1, pp 1–5). A large-scale GWAS meta-analysis discovered 49 loci for waist-to-hip ratio adjusted for BMI (to focus on fat distribution rather than total fat).[16] Gene expression enrichment for genes near these loci was seen in adipose tissue, suggesting that fat distribution is largely regulated in local fat depots. These 49 loci explain 1·4% of the variance in waist-to-hip ratio overall (2·4% in women and 0·8% in men).

Although most GWAS were done in adults, the Early Growth Genetics (EGG) consortium and others have examined birthweight, BMI, and common obesity in children, and early-onset extreme obesity (appendix 1). GWAS for childhood BMI and common obesity have identified many of the same loci as in adult GWAS. By contrast, birthweight and early-onset extreme obesity are largely driven by unique loci, although they share some genetic determination with BMI and general obesity (figure 1, appendix 2).

Appendix 2 summarises the GWAS loci discovered for obesity-related traits at the genome-wide significance level ($p<5\times10^{-8}$),[17] presented to facilitate future research. Figure 1 shows these loci, grouped by families of traits. Loci for waist-to-hip ratio generally do not overlap with loci for BMI, suggesting independent regulation of fat distribution from total adiposity. The central roles of the *FTO* and *MC4R* loci are apparent in their overlap as loci for multiple adiposity traits. Future work to identify the mechanisms underlying specific loci shared among several traits (eg, *PBRM1*) might be particularly informative.

In addition to conventional GWAS, unique methods have been applied to discover genetic determinants of obesity-related traits, including consideration of parent-of-origin effects,[18] gene-based GWAS,[19] SNPs associated with variance of BMI,[20] and use of specialised fine-mapping arrays.[21–23]

Necessity of functional characterisation of genetic associations

Before a genetic variant can be leveraged to develop new therapies, its function must be characterised. This involves identification of the gene or genes whose expression is affected by alleles at the variant, and the mechanism (eg, enhancer, repressor, epigenetic alteration) whereby the variant's alleles differentially affect expression. The next step is elucidation of how the target gene affects the trait of interest. A common convention has been to use names of the nearest genes to assign names to SNPs found in GWAS. This can be misleading, as SNPs could exert their effect on a phenotype by affecting expression of genes at considerable distances. The *FTO* story is instructive: *FTO* encodes a 2-oxoglutarate-dependent nucleic acid demethylase that is ubiquitously expressed but most highly expressed in hypothalamic nuclei governing energy balance.[24] A large body of research on *FTO* has found conflicting results.[25,26] For example, both *FTO*-knockout and *FTO*-overexpressing mice show hyperphagia.[27,28]

FTO SNPs appear to affect the expression of other genes.[25,26] Chromatin conformation analysis found that these SNPs physically contact the promoter of a distant gene, *IRX3*.[29] Studies in mesenchymal adipocyte precursors suggested that the risk allele at the *FTO* SNP rs1421085 disrupts a binding site for the ARID5B repressor, leading to increased expression of *IRX3* and *IRX5*, which shifts the fate of these cells from energy-burning beige adipocytes to energy-storing white adipocytes.[30] Other studies suggested that the obesogenic effects of *FTO* SNPs on *IRX3* operate in the brain[29] or the pancreas.[31] Studies in neural cells found that the risk 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 consequent reduced leptin signalling.[32,33] The effects of the *FTO* locus on distant genes might therefore be tissue-specific and vary by the developmental stage of the tissue. Whether effects in the brain, adipose tissue, and pancreas all contribute to obesity or whether an effect in a particular tissue is the primary effect remains to be established. Future efforts to develop treatments (or prevention strategies) for obesity might require targeting

of *IRX3*, *IRX5*, or *RPGRIP1L*, or a combination of these. Studies of other loci for obesity have not yet reached the level of molecular resolution achieved for *FTO*,[34] but this knowledge will be realised in time. A deep understanding of how a locus affects phenotype is essential before genetic findings can be used to improve human health. For loci that encompass multiple genes, bioinformatics tools are emerging to help select the most promising SNPs and genes for initial functional interrogation.[35,36]

Gene by environment interactions in obesity

Gene by environment interaction studies are presented with the caveat that such analyses are susceptible to confounding, in part because of the heterogeneity of studies included in meta-analyses, bias in self-reported environmental data, failure to account for the distribution of BMI, and because genetic variants could have larger effects in groups of individuals with higher BMI.[37] Methodological challenges in gene by environment interaction studies have been extensively reviewed.[38] These challenges notwithstanding, several studies outlined here suggest that individuals with the greatest genetic predisposition to obesity are more susceptible when exposed to adverse environments, indicating that potentially harmful lifestyle factors do not affect the population equally. Epigenetic modifications might mediate the effects of the environment on genetic associations.[38]

Gene by obesogenic environment interactions

The past four decades have witnessed a substantial increase in obesity. Our genes have not changed in this timeframe; what has changed is our environment and lifestyle. If our environment has become more obesogenic than in previous decades, this raises the question of whether genetically predisposed individuals are more susceptible to obesity in this environment. Among 8788 adults born between 1900 and 1958, the association 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.[41] This finding is consistent with the general environment having become more obesogenic than in previous years, interacting with genetics to magnify the association of genetic risk scores with BMI. In the Framingham Heart Study, the association of *FTO* with BMI was greater in later birth cohorts than in earlier cohorts, with an inflection point at the birth year 1942.[42] In around 900 individuals born between 1901 and 1986, a 32-SNP BMI genetic risk score showed positive interaction by birth year for BMI, waist circumference, and skinfold thickness.[43] Even monogenic disorders such as *MC4R* deficiency appear to be increasingly penetrant in recent generations.[44]

A GWAS meta-analysis (including more than 320 000 individuals) of SNP by age interactions found 15 loci (including *FTO*) with age-modified effects on BMI, of which 11 showed a greater effect on BMI in individuals younger than 50 years.[45] Presumably some of these effects reflect our increasingly obesogenic environment, whereas others might reflect a biological effect of ageing or an increasing non-genetic influence with ageing (ie, accumulating effects of environmental factors). A study of more than 8000 individuals from the Framingham Heart Study suggested that both possibilities coexist.[46] A longitudinal study of individuals born during 1 week found that a genetic risk score based on 11 SNPs associated with adult BMI was associated with weight gain in childhood but not weight gain in adulthood.[47] A systematic review concluded that the genetic contribution to BMI might be greater in children than in adults.[48]

Analyses of the UK Biobank (comprising up to 120 000 European individuals with a genetic risk score of 69 BMI SNPs) concluded that no single environmental factor, of 12 examined, was singularly responsible for the increased association of genetic risk score with BMI in the obesogenic environment.[37] A composite of factors (physical activity, sedentary time, television watching, and western diets) showed interaction with the genetic risk score on BMI.

If modernisation is obesogenic, magnified effects of obesity-related variants in urban versus rural settings

Panel 1: The genetic risk score as a key tool in the use of genetic information to elucidate biology

BMI is affected by many loci with small effects. Looking at the first 32 loci to be identified for BMI,[7] the effect sizes are modest, with most having an effect of 0·06–0·33 kg/m² per BMI-increasing allele and *FTO* having the largest effect (0·4 kg/m² per allele).[39] To create a genetic tool with more power than individual variants, investigators have aggregated variants into genetic risk scores, which are the sum of risk-increasing alleles, often weighted by the effect sizes from the studies that discovered them. In the case of BMI, a genetic risk score is the sum of BMI-increasing alleles (0, 1, or 2) at each of the single-nucleotide polymorphisms (SNPs) robustly associated with BMI.

Many studies constructing genetic risk scores for BMI used the 32 SNPs reported in the 2010 GIANT meta-analysis.[7] A BMI genetic risk score based on these 32 loci was generated in more than 8000 individuals.[39] As often observed for genetic risk scores of other traits, the genetic risk score values followed a bell-shaped distribution; although the possible range of the genetic risk score was 0 to 64, the observed range was 16 to 44. BMI was 3 kg/m² higher for those at the top of the distribution (genetic risk score ≥38) than for those at the bottom (genetic risk score ≤21), with each unit increment in genetic risk score associated with nearly 0·2 kg/m² higher BMI.

Simulations have found that genetic risk scores have greater power than individual SNPs for detection of interactions with environmental factors.[40] As described herein, the genetic risk score has proven to be an excellent tool for elucidating biology through genetics. Not only is the genetic risk score a more powerful construct than single variants from a statistical standpoint, it is also appealing because it reflects how genetics affects traits in individuals—each person's genetic risk is affected by the collection of risk-increasing alleles inherited from their parents. Most SNPs incorporated into genetic risk scores were discovered in Europeans, possibly limiting their applicability to other populations. This Series paper focuses mainly on studies that used genetic risk scores or the *FTO* variant; studies of other loci are presented if particularly informative.

would be expected. Nominal evidence for such gene by urban environment interaction has been reported for *FTO* in South Asians.[49,50] Similarly, a Korean study suggested that an urban versus rural environment could modify genetic effects on abdominal adiposity.[51]

Gene by smoking interactions

No interaction between smoking and *FTO* on BMI has been observed.[52] SNP rs1051730 in the *CHRNA5–CHRNA3–CHRNB4* gene cluster that is robustly associated with smoking quantity in smokers was associated with lower BMI only in smokers, suggesting a causal effect of smoking to decrease BMI.[53] GWAS in a Pakistani cohort identified a novel SNP in the *FLJ33534* locus whose effect was modified by smoking, with the minor allele associated with lower BMI in current smokers and with higher BMI in never smokers.[54] In another study, SNPs near *MC4R* and *POC5* nominally showed interaction with smoking on adolescent BMI in European Americans and one SNP near *TNNI3K* showed a strong interaction in Hispanic Americans.[55] For all three SNPs, the association with BMI was increased in smokers. This seems counterintuitive since smoking is associated with decreased BMI and people who quit smoking often gain weight.[56] A study of 95 BMI SNPs in around 8000 Pakistani adults found nominal interactions for four SNPs, three of which amplified the association with BMI in smokers.[57] A large-scale GWAS meta-analysis identified 23 novel associations accounting for smoking and nine loci with gene by smoking interactions on BMI, waist circumference, and waist-to-hip ratio.[58] Genes near the novel loci are involved in addictive behaviour and oxidative stress, and the *CHRNA5–CHRNA3–CHRNB4* interaction was replicated. SNPs explained more variance for BMI in smokers than in non-smokers, whereas SNPs explained more variance for waist-to-hip ratio in non-smokers than in non-smokers. In summary, several studies have reported that smoking could magnify the association of specific BMI-related SNPs with BMI, and dampen the association of waist-to-hip ratio SNPs with waist-to-hip ratio. These results suggest that, although smoking in general could have an effect on reducing BMI, in those at highest genetic risk for obesity smoking cessation might be recommended to reduce this risk.

Gene by alcohol interactions

Genetic regulation of BMI might differ in the setting of alcohol dependence.[59] The Glu504Lys (rs671) variant in *ALDH2* (mitochondrial) has been associated with alcohol intolerance in around 50% of East Asians who lack activity of this enzyme, resulting in uncomfortable symptoms after alcohol intake.[60] Not surprisingly, the Lysine allele has been associated with reduced alcohol intake.[61] In terms of interaction with obesity phenotypes, a study of 2958 Chinese individuals found that the Glu504Lys (rs671) variant was associated with visceral fat only in regular consumers of alcohol, wherein lower alcohol consumption in Lysine allele carriers might result in reduced visceral adiposity.[62] In another study, increasingly frequent alcohol consumption dampened the association of *FTO* with BMI.[52]

Gene by socioeconomic status interactions

Among approximately 9000 non-Hispanic European individuals, persistently low socioeconomic status or downward mobility (decreasing socioeconomic status over time) nominally magnified the association of a 29-SNP genetic risk score with BMI, whereas persistently high socioeconomic status or upward mobility dampened the association.[63] Similar results for socioeconomic position and genetic risk score were observed in the UK Biobank study, where the Townsend deprivation index appeared to best represent the obesogenic environment.[37]

Other gene by environment interactions

Chronic psychosocial stress could also interact with genetic predisposition to affect adiposity phenotypes.[64,65] It has also been shown that increased deviation from mean sleep duration magnified the association of *FTO* with BMI.[52] However, robust interactions were not observed between individual GWAS SNPs and completed college education[66] or between a 69-SNP genetic risk score and years of education in terms of modifying association with BMI or adiposity.[37]

Gene by sex interactions in obesity

The best known gene by sex interactions are the several loci associated with waist-related phenotypes more strongly (or solely) in women than in men.[16,67] A large-scale genome-wide interaction study found 44 loci for waist-to-hip ratio (adjusted for BMI) that exhibited sexual dimorphism, 28 of which had larger effects in women, five had larger effects in men, and 11 had opposite effects in women and men.[45] This study found no interaction between sex and BMI loci. By contrast, in a large GWAS meta-analysis in individuals of Asian ancestry, four novel loci for BMI were reported, of which two (*KCNQ1* and *ALDH2*) showed stronger associations in men than in women.[68] A subsequent targeted analysis of BMI, waist circumference, and waist-to-hip ratio variants in 2958 Chinese individuals found associations of *MC4R* with visceral fat area and of *LYPLAL1* with subcutaneous fat area in women only and associations of *ALDH2* with visceral fat area in men only.[62] GWAS meta-analysis in individuals of African ancestry discovered three loci for BMI and four loci for waist-to-hip ratio showing sexual dimorphism.[69] These studies raise the possibility that gene by sex interactions might depend on ancestry.

Gene by lifestyle interactions in obesity

Gene by diet interactions

Many studies have associated sugar-sweetened beverage intake with weight gain and related complications such as diabetes. 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 (21740 women) found that increased intake of sugar-sweetened beverages amplified the association of a 32-SNP genetic risk score with BMI, with the genetic effect approximately doubled when comparing the lowest with the highest sugar-sweetened beverage intake.[70] Additionally, in those with higher genetic risk scores, the association of sugar-sweetened beverage intake with BMI was stronger than in those with lower genetic risk scores. Similar interaction effects between genetic risk score and sugar-sweetened beverage intake were seen for incident obesity.[70] However, in a study of the UK Biobank, comprising around 46 000 individuals, no interaction between a 69-SNP BMI genetic risk score and so-called fizzy drink intake on BMI was observed.[37]

The Nurses' Health Study, Health Professionals Follow-up Study, and Women's Genome Health Study cohorts were used similarly to show that the association of the 32-SNP genetic risk score with BMI was amplified in those with increased fried food intake.[71] Additionally, the effect of fried food consumption on BMI was greater in individuals with higher genetic risk scores than in those with lower genetic risk scores. This effect of fried food consumption was not seen in the UK Biobank.[37]

A large-scale analysis for gene and diet (assessed as a composite healthy diet score) interaction used a genetic risk score composed of 32 BMI-associated SNPs and a genetic risk score composed of 14 waist-to-hip ratio-associated SNPs.[72] In this meta-analysis,[72] a significant genetic risk score by healthy diet score interaction was not seen for the BMI-associated genetic risk score with BMI, while nominally significant interactions were seen for the waist-to-hip ratio genetic risk score and healthy diet score with waist-to-hip ratio adjusted for BMI. In contrast to the studies described above,[70,71] in which unhealthy dietary factors amplified the association of genetic risk score with obesity-related traits, the association of genetic risk score with waist-to-hip ratio in the meta-analysis[72] was greater in magnitude with higher healthy diet scores. The authors raised biased self-reporting of diet as a possible explanation for this counterintuitive result. If future studies substantiate an increased genetic effect on waist-to-hip ratio in the setting of healthy diet factors, this might reflect differential gene by diet regulation of fat distribution (waist-to-hip ratio) versus total adiposity (BMI). The composite healthy diet score might have obscured from detection significant gene by diet signals for individual diet components. Other studies looking at non-specific dietary factors (total energy, fat, carbohydrate, protein, or fibre) found no genetic risk score by diet interactions on adiposity measures.[37,73] Although some studies on *FTO* found that its association with BMI was enhanced in settings of higher caloric intake,[74,75] higher protein intake,[76] higher saturated fat intake,[77,78] and in those who add salt to their food,[52] a large study (177 300 adults) found no interactions on BMI between *FTO* and total energy, protein, carbohydrate, or fat intake.[79]

Gene by physical activity interactions

In more than 20 000 individuals, physical activity dampened the effect of a 12-SNP genetic risk score on BMI and on the odds of obesity.[80] Similarly, in 2444 participants, physical activity at the age of 36 years dampened the association of an 11-SNP genetic risk score with BMI at the same age, and physical activity at 53 years attenuated the association of the genetic risk score with the rate of change in BMI from 53 years to 63 years.[81] In more than 109 000 individuals in the UK Biobank, physical activity dampened the association of a 69-SNP genetic risk score with BMI.[37] These results suggest that physical activity can overcome an adverse genetic profile for obesity. Those with the greatest genetic risk of obesity (higher genetic risk scores) benefited the most from physical activity, including low levels of activity, in all aforementioned studies.

A meta-analysis (comprising 111 421 individuals of European ancestry) found a nominally significant 12-SNP genetic risk score by physical activity interaction on BMI, which was primarily driven by individuals from the American cohorts and not seen in the European cohorts,[82] raising the possibility of population-specific interaction effects. In the US Framingham Heart Study, an attenuating effect of physical activity on the genomic effect on BMI was seen in individuals aged 21–50 years.[46] In a cohort of 2894 Chinese Han individuals, increased physical activity nominally attenuated the association of a 28-SNP genetic risk score with BMI.[83] Conversely, among around 8000 Pakistani individuals, a 95-SNP genetic risk score showed no interaction with physical activity on BMI.[57] It is unclear why a genetic risk score by physical activity interaction would be present in American and Chinese populations but not in European or Pakistani populations. Because the interaction has been seen in some European cohorts,[80] further studies are warranted to ensure these differences did not arise by chance.

Analysis of a 32-SNP BMI genetic risk score in the Nurses' Health Study and Health Professionals Follow-up Study also found that leisure time spent on physical activity attenuated the association of the genetic risk score with BMI.[84] This study also found that the association of the genetic risk score with BMI was amplified in the setting of increased sedentary behaviour (measured as weekly hours of television watched). The interactions of genetic risk score with physical activity and with sedentary behaviour were independent of each other. This finding suggests that physical activity and sedentary behaviour are two distinct targets for management of obesity. In around 120 000 individuals in the UK Biobank study, sedentary time and hours spent watching television were separately assessed for genetic risk score interaction on BMI; sedentary time showed a strong interaction while watching television showed a nominal interaction.[37]

Several studies have focused on the interaction between the *FTO* locus and physical activity, with conflicting results. The most definitive study is a meta-analysis of 218 166 adults and 19 268 children and adolescents.[85] Interaction between *FTO* genotype and physical activity was seen only in adults, where the odds of obesity were 1·30 per obesogenic allele in the inactive group and 1·22 per allele in the active group, representing a 27% reduction in risk with physical activity. In a prospective multiethnic cohort, of 14 BMI SNPs examined, physical activity attenuated the effect of only *FTO* on baseline and follow-up (median 3·3 years) BMI and body adiposity index.[86] A genome-wide interaction meta-analysis of 200 452 adults (90% European) identified only *FTO* as having its effect on BMI modified by physical activity; no interaction effects on waist circumference or waist-to-hip ratio were observed.[87]

These studies show that physical activity can dampen the effect of adverse genetics on the risk of obesity. Thus, those at highest risk should be properly counselled to adopt an active lifestyle. Direct-to-consumer genetic profiling has made it possible for individuals to learn their risk on the basis of GWAS variants. However, without proper counselling, provision of such information can have unintended consequences. A meta-analysis of genetic risk-based counselling across multiple conditions found that knowledge of genetic risk generally does not change behaviour.[88] Counselling based on genetic risk of obesity typically resulted in reduced self-blame and increased motivation to make lifestyle changes in high-risk individuals, yet did not result in weight loss.[89–91] In one study, those who found out that they had an increased genetic risk of obesity subsequently, on average, increased their fat intake and engaged in less leisure-time exercise than they did previously.[92] Thus, the very people who stood the most to gain from an improved lifestyle responded in the opposite way after learning their genetic risk, perhaps feeling that they were doomed by their genetics. In the future, when personalised genomic profiling becomes routine, it is anticipated that high risk individuals, with proper counselling, would intensify rather than de-intensify their lifestyle. This raises the key question of whether adverse obesity genetics might impair the ability of individuals to lose weight.

Gene by weight loss intervention interactions

Studies have assessed whether genotype modifies the effect of diet, exercise, or drug intervention on weight loss. This is a different gene by lifestyle interaction (with the outcome being weight loss) to that described earlier (where the outcome was BMI or obesity). Results from intervention trials (typically with modest sample sizes) have been conflicting about the effect of *FTO* genotype on response to a weight loss intervention. A meta-analysis[93] of individual patient-level data from eight randomised controlled trials found no effect of *FTO* genotype on the response of BMI, weight, or waist circumference to diet-based, drug-based, or exercise-based weight loss interventions. In the Diabetes Prevention Program,[94] a 16-SNP genetic risk score had no interactions with treatment modality in weight loss or weight regain. In a Danish trial[95] of intensive lifestyle intervention, a 30-SNP genetic risk score was associated with bodyweight at baseline but not with change in weight; no interaction between genetic risk score and physical activity on weight change was observed. In the Look AHEAD trial assessing an intensive lifestyle intervention in overweight and obese people with type 2 diabetes,[96] none of 13 SNPs examined was associated with weight loss at 1 year, although an interaction between *FTO* genotype and treatment group on weight regain was observed. However, in a joint analysis of the Diabetes Prevention Program and Look AHEAD, none of 91 obesity SNPs were associated with weight loss or regain after consideration of multiple testing.[97] In the DIOGENES study of 651 SNPs in 69 genes, including *FTO*, no association of the SNPs with weight regain after a low-calorie diet was found.[98] Overall, these studies suggest that BMI SNPs should not interfere with the success of lifestyle-based weight loss interventions, especially intensive efforts, representing another important message for genetic counselling.

For bariatric surgery, the few available studies have been too small to provide conclusive evidence of gene by intervention interactions. The largest interaction study to date found one SNP in *FTO*, rs16945088, that modulated weight loss after gastric banding but not gastric bypass; this SNP is not in linkage disequilibrium with *FTO* SNPs identified in GWAS for obesity-related traits and the GWAS-discovered *FTO* SNPs were not associated with weight loss after surgery.[99] Additional and larger studies are needed of gene by surgery interactions on weight loss.

Genetic variants in obesity used as tools to assess causality

In addition to elucidating the biology of obesity itself, GWAS loci (typically *FTO* or genetic risk score) have provided useful tools to examine causal associations between obesity and conditions for which epidemiological studies suggest that obesity is a risk factor. In observational studies, obesity has been linked to numerous complications; however, association does not prove causality. The association might reflect reverse causation or be mediated by other (sometimes unmeasured or unknown) factors that influence both obesity and the complication. In mendelian randomisation or instrument variable analysis, the risk factor (in this case, obesity) is replaced by genetic loci for that risk factor and analysed for its ability to predict the outcome or complication. As genetic variants are not altered by confounding phenotypes or reverse causality, this analysis allows assessment of whether the risk factor has a causal association with the outcome. For this approach to

succeed, the instrument variable must also be a valid representation of the predictor variable. Additionally, the genetic variants for the risk factor must not associate with potential confounders or be in linkage disequilibrium with SNPs associated with other risk factors (pleiotropy). Whether *FTO* and BMI genetic risk scores are sufficiently free of pleiotropy is still under debate.[100] Population stratification (chance genetic differences between cases and controls, often arising from unrecognised ancestral differences) can also bias mendelian randomisation analyses. The most robust mendelian randomisation analyses address all of the above issues explicitly.[101]

Formal analyses integrate epidemiological association with genetic association to calculate the causal association between the risk factor and the outcome (ie, the effect of genetically increased BMI on the outcome). Less formal analyses examine only the association between genetic loci for the risk factor and the outcome, or they examine loci that associate with both the risk factor and the outcome (eg, overlapping loci from GWAS for both). This Series paper focuses mainly on studies that used formal mendelian randomisation analyses to explore mediation between obesity and other traits. Other models, such as pleiotropy and moderation, which might apply to obesity loci, are not discussed. Although not absolutely definitive, mendelian randomisation has been highly informative about the causality of obesity for many traits.

Cardiometabolic risk factors and events

Mendelian randomisation analyses in this setting have generally produced expected causal associations of BMI with metabolic traits (table 1; appendix 1, p 6). Evidence for causality of BMI has been mixed for fasting glucose and LDL cholesterol. Repeated causal associations of BMI with type 2 diabetes and fasting insulin are consistent with the prevailing view that obesity can cause diabetes by exacerbating insulin

	Timpson et al (2009)[102]	Fall et al (2013)[103]	Afzal et al (2014)[104]	Holmes et al (2014)[105]	Fall et al (2015)[106]	Millard et al (2015)[107]	Wang et al (2016)[108]
Sample size	37 027	>198 000	96 423	34 538	67 553	8121	2884
Instrument	*FTO*, *MC4R* SNPs	*FTO* SNP	*FTO*, *MC4R*, and *TMEM18* SNPs	GRS of 14 BMI SNPs	GRS of 32 BMI SNPs	GRS of 31 BMI SNPs	GRS of 38 BMI SNPs; GRS of 13 WHR SNPs
Type 2 diabetes	..	+	+	+	..	..	..
Fasting glucose	..	NS	..	+	..	+	..
2 h glucose	..	+	..	..	..	..	..
Fasting insulin	..	+	..	+	+	+	..
HbA_{1c}	..	NS	..	..	..	..	..
Insulin secretion	..	..	..	..	..	..	+ (BMI)
Insulin resistance	..	..	..	..	..	..	+ (WHR)
Systolic blood pressure	+	+	..	+	+	+	..
Diastolic blood pressure	+	+	..	..	+	..	..
Hypertension	..	+	..	..	..	..	..
Total cholesterol	..	NS	..	..	..	NS	..
LDL cholesterol	..	NS	..	–	..	NS	..
HDL cholesterol	..	–	..	–	–	– (Bonf)	..
Triglycerides	..	+	..	..	+	+ (permut)	..
VLDL cholesterol	..	..	..	..	..	+ (permut)	..
Apolipoprotein A-I	..	..	..	..	..	+ (permut)	..
Apolipoprotein B	..	..	..	..	..	+ (permut)	..
C-reactive protein	..	+	..	..	+	+	..
Interleukin 6	..	NS	..	+	+	+ (permut)	..
Leptin	..	..	..	..	..	+	..
Adiponectin	..	..	..	..	..	NS	..
Alanine aminotransferase	..	+	..	..	..	..	..
γ-glutamyltransferase	..	+	..	..	..	..	..
Metabolic syndrome	..	+	..	..	..	..	..

SNP=single-nucleotide polymorphism. GRS=genetic risk score. WHR=waist-to-hip ratio. NS=no causal association of BMI with the trait was observed. Bonf=association was significant with Bonferroni correction for multiple testing. permut=association was significant in permutation testing. + indicates that a positive causal association of BMI for the trait was observed. – indicates that an inverse causal association of BMI for the trait was observed. Empty cells (indicated by "..") indicate traits that were not tested in a particular study.

Table 1: **Mendelian randomisation studies assessing causality of obesity for cardiometabolic traits**

	Cohort	Instrument	Conclusion
Nordestgaard et al (2012)[112]	11 056 coronary heart disease events in 75 627 individuals	GRS of three BMI SNPs (*FTO*, *MC4R*, *TMEM18*)	BMI is causal for coronary heart disease: 52% increased odds of coronary heart disease with every genetic increase in BMI of 4 kg/m²
Klovaite et al (2015)[113]	87 574 Danish adults, 2158 with deep vein thrombosis and 299 with deep vein thrombosis in the setting of pulmonary embolism	*FTO* (rs9939609)	Increased BMI is not causal for deep vein thrombosis without pulmonary embolism and might be causal for deep vein thrombosis with pulmonary embolism
Hagg et al (2015)[111]	Up to 22 193 individuals with 3062 incident cardiovascular events	GRS of 32 BMI SNPs	Increased BMI is causal for incident heart failure, ischaemic stroke, and coronary heart disease (coronary heart disease required additional samples from CARDIoGRAMplusC4D)
Cole et al (2016)[110]	5831 cases of early onset coronary artery disease and 3832 controls	GRS of 35 BMI SNPs	Increased BMI is causal for early coronary artery disease
Chatterjee et al (2017)[114]	51 646 individuals of European origin from seven prospective cohorts, with 4178 incident cases of atrial fibrillation	*FTO* and a GRS of 39 BMI SNPs	Causal association observed for BMI, with each unit increase in the GRS increasing the hazard ratio for atrial fibrillation by 11%
Huang et al (2016)[115]	11 477 Chinese adults with measures of ankle-brachial index	GRS of 14 BMI SNPs	BMI is causal for peripheral arterial disease

GRS=genetic risk score. SNP=single-nucleotide polymorphism.

***Table 2*: Mendelian randomisation studies primarily assessing causality of obesity on cardiovascular events**

	Cohort	Instrument	Conclusion
Guo et al (2016)[117]	62 328 individuals with breast cancer, 83 817 controls (from two cohorts)	GRS based on 84 BMI variants	Increased BMI reduces breast cancer risk in premenopausal and postmenopausal women
Gao et al (2016)[118]	Genetic Associations and Mechanisms in Oncology (GAME-ON) Consortium (51 537 individuals with cancer and 61 600 controls)	GRS of seven SNPs for birthweight; GRS of 15 SNPs for childhood BMI; GRS of 77 SNPs for adult BMI; 14 SNPs for adult WHR	Increased BMI (childhood or adult) reduces breast cancer risk; increased adult BMI is causal for lung, ovarian, and colorectal cancer; BMI is not causal for prostate cancer
Benn et al (2016)[119]	108 812 individuals (Danish general population), median 4·7-year follow-up, multiple cancers	GRS of five BMI SNPs	BMI is not causal for lung, breast, prostate, colon, kidney, skin, or any other cancer (limited power for several cancers)
Carreras-Torres et al (2016)[120]	16 572 individuals with lung cancer, 21 480 controls	GRS of up to 96 BMI SNPs	Increased BMI is causal for squamous-cell and small-cell carcinoma, but not for adenocarcinoma
Dixon et al (2016)[121]	Ovarian Cancer Association Consortium (39 studies; 14 047 individuals, 23 003 controls)	GRS of 87 BMI SNPs	Increased BMI is causal for non-high grade serous ovarian cancers but not for high grade serous ovarian cancer
Jarvis et al (2016)[122]	Up to 18 190 individuals with colorectal cancer and 27 617 controls (of European ancestry)	GRS of 76 BMI SNPs; GRS of 14 WHR SNPs; GRS of nine SNPs for childhood obesity; GRS of seven SNPs for birthweight	BMI, WHR, and childhood obesity are causal for colorectal cancer
Thrift et al (2015)[123]	10 226 individuals with colorectal cancer, 10 286 controls (of European ancestry)	GRS of 77 BMI SNPs	Causal association of increased BMI for colorectal cancer, only in women in sex-stratified analysis
Davies et al (2015)[124]	20 848 individuals with prostate cancer and 20 214 controls	GRS of 32 BMI variants	Increased BMI is not causal for incidence of prostate cancer, but is associated with increased all-cause mortality among men with low grade disease
Thrift et al (2014)[125]	999 patients with oesophageal adenocarcinoma, 2061 patients with Barrett's oesophagus, and 2169 population controls	GRS of 29 BMI variants	Increased BMI is causal for oesophageal cancer and its precursor Barrett's oesophagus
Nead et al (2015)[126]	1287 individuals with endometrial cancer and 8273 controls	GRS of 32 BMI variants	Increased BMI is causal for endometrial cancer
Painter et al (2016)[127]	6609 individuals with endometrial cancer and 37 926 controls	GRS for BMI (77 SNPs) and WHR (47 SNPs)	Increased BMI, but not WHR, is causal for endometrial cancer
Carreras-Torres et al (2017)[128]	7110 individuals with pancreatic cancer and 7264 controls	GRS of 95 BMI SNPs	Increased BMI is causal for pancreatic cancer

GRS=genetic risk score. SNP=single-nucleotide polymorphism. WHR=waist-to-hip ratio.

***Table 3*: Mendelian randomisation studies assessing causality of obesity for cancer**

resistance. Mendelian randomisation and simple association studies have suggested that total adiposity (BMI) mainly influences insulin secretion, whereas fat distribution (waist-to-hip ratio) influences insulin resistance;[108,109] increases in both insulin secretion and insulin resistance should result in increased fasting insulin. The consistent causal associations of BMI with other components of the metabolic syndrome (blood pressure, triglycerides, and HDL cholesterol) suggest that obesity might be the root cause of the syndrome.

The association of obesity with numerous cardiovascular risk factors raises the question of whether obesity is causal

for cardiovascular disease events directly (acting via body mass) or indirectly (eg, given its association with lipids). For coronary heart disease, the balance of evidence[110–112] supports BMI as a causal factor (table 2). In two studies[103,105] that did not find BMI to be causal for coronary heart disease, coronary heart disease was one of many traits examined; also, one of the studies[103] used only *FTO* as the instrument variable and the other[105] showed some suggestion of causality. A mediation analysis suggested that a portion of the effect of obesity on coronary heart disease is mediated by LDL cholesterol, remnant cholesterol, and systolic blood pressure (7–8% each), with no mediating effect of decreased HDL cholesterol or raised C-reactive protein.[116] Evidence is mixed for stroke, whereas mendelian randomisation studies have concluded that obesity is causal for heart failure, atrial fibrillation, and peripheral arterial disease (table 2; appendix 1, p 6). Studies of genetic risk scores are needed to assess whether obesity is causal for cardiovascular or all-cause mortality.

Cancer

A potential causal role of obesity has been long recognised for various forms of cancer. Breast cancer is unique in its inverse association with BMI. For most other cancers examined (table 3), increased BMI is causal for increased risk of cancer, with the notable exception of prostate cancer. 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.

Psychiatric and neurological traits and disorders

Genetics has been used to interrogate the potential causal role of obesity in several neuropsychiatric traits and disorders (appendix 1, p 7). Reverse causality is a particular concern in several of these states; for example, people with depression or schizophrenia might adopt lifestyles or take medications (eg, atypical antipsychotics) that promote weight gain. Mendelian randomisation studies support a causal role of obesity in multiple sclerosis and have ruled it out for Alzheimer's disease, bipolar disorder, and schizophrenia. Current evidence does not support a causal role for obesity in depression. A seemingly paradoxical effect of increased BMI on reduced psychological distress awaits confirmation.[129]

Reproductive traits and disorders

Obesity influences reproductive health; mendelian randomisation has been applied to explore causality (appendix 1, p 8). Studies have suggested a shared genetic basis between obesity and timing of puberty.[130] Age of menarche has become progressively lower in approximately the past 50 years, possibly linked to the concurrent obesity epidemic. Among 8156 women, mendelian randomisation analysis suggested that BMI in childhood was causal for menarche occurring before the age of 12 years.[131] However, in 556 children, a 42-SNP genetic risk score for age of menarche was associated with BMI, raising the possibility of bidirectional causality.[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.[133]

Other traits and conditions

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 (appendix 1, p 9). Obesity is linked to numerous additional conditions, many of which have been interrogated in mendelian randomisation analyses (figure 2; appendix 1, p 10). In addition to the analyses that examined multiple cancers[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).[107,135] 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.[136–138]

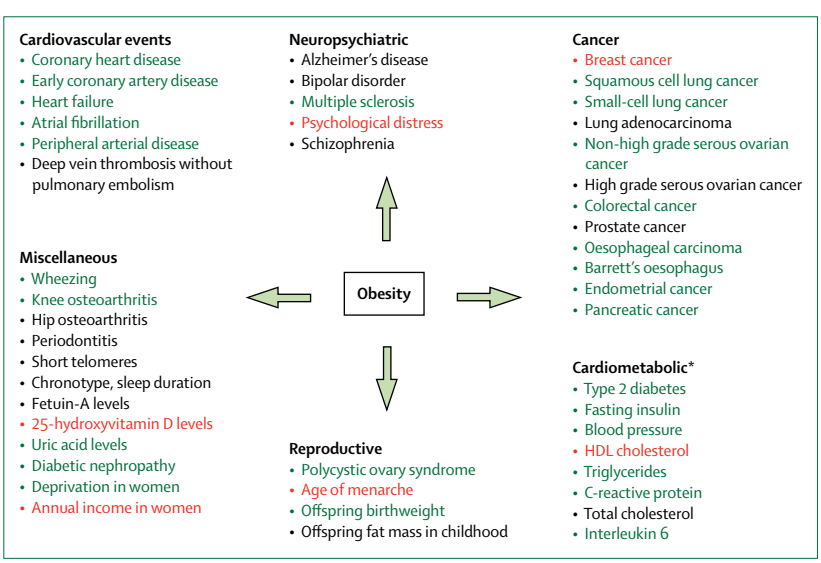

***Figure 2*: Inferences of causality of obesity derived from mendelian randomisation studies**
Traits and diseases shown in green are those for which obesity appears to have a positive causal association. Traits and diseases shown in red are those for which obesity has an inverse causal association. Black indicates traits and diseases for which mendelian randomisation studies have argued against a causal association of obesity. Traits for which evidence is mixed, available from only small studies, or observed with borderline significance are not included. *Since many cardiometabolic traits have been tested (table 1), only those with the most consistent evidence across studies are shown.

Panel 2: Can genetic findings lead to treatments for obesity?

With the discovery of more than 300 loci for BMI and adiposity-related traits, there is hope that new drugs to prevent or treat obesity will be developed on the basis of these findings. The case of type 2 diabetes is illustrative. For three different classes of diabetes medication (sulfonylureas, thiazolidinediones, and glucagon-like peptide-1 receptor agonists), the molecular targets are coded by genes (*ABCC8* and *KCNJ11* for sulfonylureas, *PPARG* for thiazolidinediones, and *GLP1R* for glucagon-like peptide-1 receptor agonists) identified by large-scale genetic association studies of type 2 diabetes.[143] In these cases, the drugs preceded gene discovery. Among more than 150 loci for type 2 diabetes and related quantitative traits, additional effective drug targets almost certainly exist. Of note, these examples (and others; eg, *HMGCR* and cholesterol levels) show that the effect size of the association between an SNP and a trait does not predict whether the responsible gene will be a valuable drug target.

Although not as clear as the examples for type 2 diabetes, three drugs used for weight loss (sympathomimetics, bupropion, and topiramate)[144] might act on targets coded by genes (*ADRB1* for sympathomimetics, *MC4R* for bupropion, and *GRID1* for topiramate) near loci for BMI or related traits, supporting the likelihood that findings of genome-wide association studies (GWAS) will be exploited to develop future obesity treatments (eg, targeting the ARID5B–IRX3–IRX5 system). Another reason for hope is the success of genetics-based treatment of monogenic obesity disorders. Congenital leptin deficiency results in severe childhood-onset obesity due to massively increased food intake.[145] Treatment with recombinant human leptin led to appetite reduction and substantial weight loss in affected individuals.[146] In common obesity, leptin treatment has produced variable results, but in some instances it resulted in weight loss to a similar extent to available weight loss medications.[147]

Another monogenic disorder, proopiomelanocortin deficiency, leads to obesity and hyperphagia caused by deficiency of melanocyte stimulating hormone, which signals through the melanocortin-4 receptor (MC4R).[148] A new MC4R agonist, setmelanotide, led to significant weight loss in two affected adult patients.[149] If *MC4R* is found to be the mechanistic gene of action whereby common SNPs at the *MC4R* locus affect BMI, setmelanotide could potentially be used as a treatment for common obesity.

Search strategy and selection criteria

References were identified by searches of PubMed with the terms "obesity", "adiposity", "body mass index", "body fat", "fat mass", and "body fat percentage" in combination with the terms "gene", "genetic", "genetics", "genome wide association study", "GWAS", "genetic risk score", "interaction", "mendelian randomization", "mendelian randomisation", or "instrument variable". Additional articles were identified by examining the bibliographies of the identified publications. Although the search mainly focused on papers published from Jan 1, 2012, to April 30, 2017, earlier references that shaped the field or present particularly relevant or novel results are included.

Mendelian randomisation analyses have produced conflicting results on whether obesity is causal for asthma (appendix 1, p 10).[139,140] Obesity appears to be causal for features of diabetic kidney disease in type 1 diabetes.[141]

The associations of several biomarkers with BMI have been informatively clarified in a series of 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 (appendix, p 11). 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]

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 (panel 2).

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 gene by environment 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.

Declaration of interests
I declare no competing interests.

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