Using genetics to uncouple higher adiposity from its adverse metabolic effects and understand its role in metabolic and non-metabolic disease.

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Abstract

To understand the consequences of higher adiposity uncoupled from its adverse metabolic effects, we selected 37 diseases associated with obesity and genetic variants associated with different aspects of excess weight including metabolically “favourable adiposity” (FA) and “unfavourable adiposity” (UFA). Mendelian randomisation (MR) identified two sets of diseases. First, 12 conditions where the metabolic effect of higher adiposity is the likely primary cause of the disease. Here MR with the FA and UFA genetics showed opposing effects on the risk of disease, including colorectal and ovarian cancer, and gout. Second, 7 conditions where the non-metabolic effects of excess weight (e.g. mechanical effect) is likely a cause. Here MR with the FA genetics, despite leading to lower metabolic risk, and MR with the UFA genetics, were both associated with higher disease risk, including osteoarthritis and venous thromboembolism. Individuals with high BMI are at higher risk of some diseases despite being relatively metabolically healthy.

Introduction

Obesity is associated with a higher risk of many diseases, notably type 2 diabetes and other metabolic diseases such as hypertension and cardiovascular disease, but many individuals are often relatively metabolically healthy compared to others of similar body mass index (BMI). Whilst these metabolically healthier individuals may be at lower risk of some BMI-related conditions, they may be at risk of conditions that are linked to other aspects of higher BMI, such as the load-bearing effects. The burden of obesity on individuals and health care systems is very large, and in the absence of a widely applicable, sustainable treatment or effective public health measures, it is important to understand the disease consequences of obesity, and how they may be best alleviated, in more detail.

Obesity is heterogeneous – for example, for a given BMI, people vary widely in their amount of fat versus fat free mass (predominantly muscle), and their distribution of fat (predominantly subcutaneous versus ectopic). Even when there is strong evidence of causality, obesity may lead to disease through a variety of mechanisms. For example, for type 2 diabetes the adverse metabolic effects, most likely excess ectopic fat manifesting in insulin resistance and deficiency¹ leads to the condition. In contrast, for osteoarthritis, it is likely that the additional load bearing of excess adiposity leads to increased damage of the joints.

Understanding the downstream consequences of obesity, and the different mechanisms by which obesity could lead to disease, is difficult in conventional study designs². Observational studies are hard to interpret because associations may be biased from confounding, reverse causality and selection. To better understand the disease consequences of obesity, many previous studies have used the approach of Mendelian randomisation (MR)³. These studies used common genetic variants robustly associated with BMI as proxies for adiposity to assess the causal effects of higher BMI on many diseases. Provided certain assumptions are satisfied, MR is far less susceptible to the problems of observational studies. These assumptions include that genetic variants are not associated with confounders or outcomes (e.g. obesity related diseases) except through the exposure trait (here BMI)⁴.

MR studies have provided strong evidence that higher BMI leads to osteoarthritis⁵, colorectal cancer⁶⁻⁸, and psoriasis⁹, as well as metabolic conditions such as type 2 diabetes, cardiovascular disease¹⁰ and heart failure^{2,11,12}. Other MR studies indicate that higher BMI may lead to lower risk of some diseases, including postmenopausal breast cancer¹³ and Parkinson's disease¹⁴. The MR evidence that higher BMI lowers breast cancer risk is opposite to that expected from cross-sectional observational data, and may be explained by exposure to higher BMI in early compared to later life¹⁵.

Despite many tens of MR studies testing the role of higher BMI in disease, few have attempted to separate and test the different mechanisms that could lead from obesity to disease. Some MR studies have investigated the effects of fat distribution, using genetic variants associated with waist-hip-ratio (WHR) adjusted for BMI and shown that adverse fat distribution (more upper body, less lower body) leads to higher risk of metabolic disease¹⁶, some cancers¹⁷ and gastro-oesophageal reflux disease¹⁸.

We have recently used a small number of specific genetic variants to separate the metabolic from the non-metabolic effects of higher BMI. These studies used 14 variants in which the allele associated with higher BMI is also associated with lower risk of metabolic disease and a favourable metabolic profile (lower triglycerides, higher HDL-cholesterol, higher sex hormone-binding globulin (SHBG) and lower levels of circulating markers of liver fat). These circulating biomarkers are all well-established as markers of metabolic health and have been used in previous studies characterising genetic variants associated with adiposity¹⁹⁻²². Using these variants

and an MR approach we found evidence that higher adiposity separated from its adverse metabolic effects leads to a higher risk of depression²³. This finding suggested that the association between obesity and depression is at least in part due to the non-metabolic effects of higher adiposity, such as poorer body image, rather than metabolic pathways²⁴.

In this study, we aimed to investigate the effects of separate components to higher adiposity on risk of metabolic and non-metabolic diseases. We used genetic variants associated with BMI and body fat percentage, and two more specific sets – those associated with higher BMI and a metabolically ‘favourable’ profile and those associated with a higher BMI and a metabolically ‘unfavourable’ profile, to understand which component of higher adiposity causes disease risk. We did so as the findings may give guidance on some obesity-related risks which are not dependent on metabolic consequences, thereby guiding appropriate medical care.

Method

Study design

An overview of our approach is shown in **Supplementary Figure 1**. First, we identified diseases by performing a literature search of studies that had used Mendelian Randomisation to assess the consequences of BMI on outcome phenotypes. We used the search terms “BMI and Mendelian randomisation” and “BMI and Mendelian randomization” (changing the spelling of randomis/zation). We identified 37 diseases associated with BMI and for which MR studies had previously been performed (**Supplementary Table 1**). We included all diseases regardless of the MR result in the published study. Second, we reperformed MR studies using BMI as an exposure. Third, for those diseases where MR indicated higher BMI was causal, we tested the effects of body fat percentage to confirm that the causal effect was due to fat mass rather than fat free mass. Fourth, for diseases where MR suggested the BMI effect was an excess adiposity effect, we used genetic variants more specific to the metabolic and non-metabolic components of higher adiposity to help understand the extent to which these factors influence disease.

Disease outcomes

We used summary statistics from existing genome wide association studies. Among the 37 identified diseases, 25 had summary GWAS data available from both a published GWAS consortium and FinnGen²⁵ and 12 diseases had GWAS summary data available in FinnGen only. For Barrett’s oesophagus, we identified GWAS summary data from a closely related outcome, gastro-oesophageal reflux. The definition of cases and controls in published GWAS and FinnGen are available in **Supplementary Table 2a-b**.

Genetic variants

We used four sets of genetic variants as proxies of four exposures (**Supplementary Table 3**):

BMI. In the broadest category, we used a set of 73 variants independently associated with BMI at genome-wide significance ($P < 5 \times 10^{-8}$). These variants were identified in the GIANT consortium of up to 339,224 individuals of European ancestry²⁶. These variants explained 1.6% of the variance in BMI in the 339,224 UK Biobank individuals.

Body fat percentage. We identified 696 variants by performing a GWAS in the UK Biobank. We used bio-impedance measures of body fat % taken by the Tanita BC-418MA body composition analyser in 442,278 individuals of European ancestry. We used a linear mixed model implemented in BOLT-LMM²⁷ to account for population structure and relatedness. We used age, sex, genotyping platform, study centre, and the first five principal components as covariates in the model.

The BMI and body fat percentage variants were partially overlapping ($n=5$ variants) but we used exposure trait specific weights for each variant.

Favourable adiposity (FA) variants. There are 36 FA variants²⁸. These variants were identified in two steps. First, they were associated (at $P < 5 \times 10^{-8}$) with body fat percentage and a composite metabolic phenotype consisting of body fat percentage, HDL-cholesterol, triglycerides, SHBG, alanine transaminase and aspartate transaminase. These six circulating markers were selected because they are established markers of adiposity and available in the UK Biobank. Second, they formed a cluster of variants that were collectively associated with higher HDL-cholesterol, higher SHBG, and lower triglycerides and liver enzymes – paradoxical to the usual

associations between higher adiposity and these measures. These variants explained 0.2% of variance in body fat percentage in the UK Biobank.

Unfavourable adiposity (UFA) variants. There are 38 UFA variants²⁸. These variants were identified in two steps. First, they were associated (at $P < 5 \times 10^{-8}$) with body fat percentage and a composite metabolic phenotype consisting of body fat percentage, HDL-cholesterol, triglycerides, SHBG, alanine transaminase and aspartate transaminase. Second, they formed a cluster of variants that were collectively associated with lower HDL-cholesterol, lower SHBG, and higher triglycerides and liver enzymes. These variants explained 0.6% variance in body fat percentage in the UK Biobank.

Mendelian randomisation

We investigated the causal associations between the four exposures (BMI, body fat percentage, FA and UFA) and 37 disease outcomes by performing two-sample MR analysis²⁹. We used the inverse-variance weighted (IVW) approach as our main analysis, and MR-Egger and weighted median as sensitivity analyses in order to detect and partially account for unidentified pleiotropy of our genetic instruments. For BMI, we used effect size estimates from the GWAS of BMI²⁶ and for body fat percentage, FA and UFA, we used effect size estimates from the GWAS of body fat percentage (442,278 European ancestry individuals from the UK Biobank study)¹⁹.

To estimate the effects of variants on our outcome diseases, we used two main sources of data: FinnGen GWAS summary results and published GWAS of the same diseases (**Supplementary Table 2a-b**). We performed MR within each data source and then meta-analysed the results across the two datasets using a random-effects model with the R package *metafor*³⁰, where the data was available in both. For one published GWAS (the GECCO consortium), we only had information for FA and UFA variants.

To provide further MR evidence we used a third source of disease data – disease status in the UK Biobank. We ran the same models but did not meta-analyse with published GWAS and FinnGen because most of the body fat percentage, FA and UFA variants were identified in the UK Biobank and so effects may be subject to weak instrument bias when using outcomes in the UK Biobank.

We obtained heterogeneity Q statistics for each inverse-variance weighted MR and MR-Egger, and I^2 statistics for each MR-Egger analysis using the *MendelianRandomization* R package³¹. All statistical analyses were conducted using R software³².

GWAS of UK Biobank traits

The UK Biobank has been described in detail elsewhere³³ but in summary, it includes >500,000 individuals aged 37–73 years (99.5% were between 40 and 69 years of age) recruited between 2006 and 2010 from across the UK. All participants provided informed written consent and the National Research Ethics Service Committee North West-Haydock approved the study. All procedures in the UK Biobank study were conducted in accordance to the World Medical Association declaration of Helsinki ethical principles for medical research. The characteristics of the study and measures and disease outcomes we used are described in **Supplementary Table 2c**. For our GWAS studies, we used a linear mixed model implemented in BOLT-LMM to account for population structure and relatedness. We used age, sex, genotyping platform, study centre, and the first five principal components as covariates in the model.

Data availability

Published GWAS data are available from the relevant publication or upon request from the corresponding authors (**Supplementary Table 2a**). FinnGen data is available at: <https://finngen.gitbook.io/documentation/>. UK Biobank data is available upon request at: <https://www.ukbiobank.ac.uk>.

Results

We identified 37 diseases as associated with obesity and for which MR studies had previously been performed. We next used genetic variants more specific to the adiposity, metabolic and non-metabolic components of higher BMI to help understand the extent to which these factors influence disease. Once we had tested BMI and body fat percentage, we further characterised the likely causal component of higher adiposity as follows (**Supplementary Figure 1, Step 5**):

i) Diseases with evidence that the metabolic effect of higher adiposity is causal. Here MR using the UFA genetic variants indicated that higher adiposity with its adverse metabolic consequences was causal to disease, whilst MR using the FA genetic variants indicated that higher adiposity with favourable metabolic effects was protective (at $p < 0.05$). We considered the BMI component to diseases as predominantly metabolic when the MR using UFA variants indicated (at $p < 0.05$) a higher risk of disease and the MR using FA genetic variants was directionally consistent with a protective effect but was less conclusive ($p > 0.05$).

ii) Diseases with evidence that there is a non-metabolic causal effect (e.g. mechanical effect, psychological/adverse social effect). Here MR using the FA genetic variants indicated that higher adiposity without its adverse metabolic consequences was causal to disease, as well as the MR using the UFA genetic variants. We considered the BMI component to diseases as predominantly non-metabolic when the MR using UFA variants indicated (at $p < 0.05$) a higher risk of disease and the MR using FA genetic variants was directionally consistent with a risk effect but was less conclusive ($p > 0.05$). When the MR using FA genetic variants indicated (at $p < 0.05$) a higher risk of disease and the MR using UFA genetic variants was directionally consistent with a risk effect ($p > 0.05$) we considered these diseases as likely having a non-metabolic component.

We grouped these disease outcomes into eight major organ systems and cancers. Where random-effects meta-analyses were performed, the heterogeneity statistics are given in **Supplementary Table 4**.

Cardiovascular system

Diseases in this category included coronary artery disease, peripheral artery disease, hypertension, stroke, heart failure, aneurysm, atrial fibrillation, venous thromboembolism, deep vein thrombosis, and pulmonary embolism (**Table 1**). MR analysis provided evidence for a causal association between higher BMI and higher odds of eight of these diseases, the exceptions being pulmonary embolism and aortic aneurysm. For each of these 8 diseases, our MR analysis using body fat percentage as the exposure indicated that the risk was due to excess adiposity.

When comparing the MR analyses for FA and UFA, our results provided evidence that the metabolic effect of higher adiposity is contributing causally to coronary artery disease, peripheral artery disease, hypertension and stroke. In addition, our results provided evidence that the metabolic effect of higher adiposity is the predominate cause of the link between higher BMI and heart failure and atrial fibrillation. For example, the MR analyses indicated the opposite direction of effects of FA and UFA with stroke; a 1-SD higher genetically-instrumented FA was associated with 0.65 [0.52, 0.83] lower odds of stroke, while a 1-SD higher genetically-instrumented UFA was associated with 1.43 [1.23, 1.67] higher odds of stroke. In contrast, the MR analysis provided evidence that a non-metabolic effect of higher adiposity is causing venous thromboembolism and deep vein thrombosis. For example, the MR analyses indicated the same direction of effects of FA and UFA with venous thromboembolism; a 1-SD higher genetically-instrumented FA was associated with 2.52 [1.82, 3.47] higher odds of venous thromboembolism, and a 1-SD higher genetically-instrumented UFA was associated with 1.63 [1.25, 2.13] higher odds of venous thromboembolism (**Figure 1a-b, Table 1**). For stroke, our results were consistent when using sub-types of the condition (**Supplementary Figure 2a, Supplementary Table 5**).

Endocrine system

Diseases in this category included type 2 diabetes and polycystic ovary syndrome. MR analysis provided evidence for a causal association between higher BMI and higher odds of both of these diseases. Our MR analysis using body fat percentage as the exposure, indicated that the risk was due to excess adiposity.

When comparing the MR analyses for FA and UFA our results provided evidence that the metabolic effect of higher adiposity is causing type 2 diabetes and is the predominant cause of the link between BMI and polycystic ovary syndrome. For example, the MR analyses indicated opposing effects of FA and UFA with type 2 diabetes, with a 1-SD genetically-instrumented FA associated with a 0.11 [0.08, 0.16] lower odds of type 2 diabetes, while a 1-SD genetically-instrumented UFA was associated with 5.50 [4.29, 7.05] higher odds of type 2 diabetes (**Figure 1c, Table 1**).

Renal system

The disease in this category was chronic kidney disease. MR analysis provided evidence for a causal association between higher BMI and higher odds of chronic kidney disease (1.21 [1.08, 1.36]). Our MR analysis using body fat percentage as the exposure indicated that the risk was due to excess adiposity (1.25 [0.98, 1.59]).

When comparing the MR analyses for FA and UFA our results provided evidence of a metabolic effect because FA and UFA had opposing directions of the effects; a 1-SD higher genetically-instrumented FA was associated with 0.64 [0.48, 0.84] lower odds of chronic kidney disease, while there was some evidence of an association between UFA and higher odds of chronic kidney disease (1.19 [0.97, 1.45]) (**Figure 1d, Table 1**).

Musculoskeletal system

Diseases in this category included gout, osteoarthritis, rheumatoid arthritis and osteoporosis. MR analysis provided evidence for a causal association between higher BMI and higher odds of gout, osteoarthritis and rheumatoid arthritis. Our MR analysis using body fat percentage as the exposure, indicated that for all three diseases the risk was due to excess adiposity.

When comparing the MR analyses for FA and UFA our results provided evidence that the metabolic effect of higher adiposity is causing gout. For example, the MR analyses indicated opposing effects of FA and UFA with gout, with a 1-SD genetically-instrumented FA associated with 0.44 [0.29, 0.68] lower odds of gout, while a 1-SD genetically-instrumented UFA was associated with 2.49 [1.88, 3.29] higher odds of gout. In contrast, the MR analysis provided evidence that there is a non-metabolic effect of higher adiposity causing osteoarthritis and rheumatoid arthritis. For example, the MR analyses indicated the same direction of the effects of FA and UFA with osteoarthritis; a 1-SD higher genetically-instrumented FA was associated with 1.45 [1.19, 1.76] higher odds of osteoarthritis, and a 1-SD higher genetically-instrumented UFA was associated with 2.20 [1.64, 2.95] higher odds of osteoarthritis (**Figure 1e, Table 1**). For osteoarthritis, our results were consistent when using sub-types of the condition (**Supplementary Figure 2b, Supplementary Table 5**).

Gastrointestinal system

Diseases in this category included gastro-oesophageal reflux disease and cholelithiasis (gallstones). MR analysis provided evidence for a causal association between higher BMI and higher odds of both diseases. For both diseases, our MR analysis using body fat percentage as the exposure indicated that the risk was due to excess adiposity.

When comparing the MR analyses for FA and UFA our results suggested that the non-metabolic effect of higher adiposity is the predominant cause of the link between higher BMI and gallstones. For example, a 1-SD higher genetically-instrumented UFA was associated with 2.55 [1.88, 3.45] higher odds of gallstones and higher genetically-instrumented FA was associated with higher risk (1.37 [0.86, 2.19]) but with less conclusive evidence ($p>0.05$) (**Figure 1f, Table 1**). For gastro-oesophageal reflux disease, the results were less conclusive but the same direction and similar effect sizes suggested a non-metabolic effect (**Figure 1g, Table 1**).

Nervous system

Diseases in this category included depression, Parkinson's disease, multiple sclerosis and Alzheimer's disease. MR analysis provided no evidence (at $p<0.05$) for a causal association between BMI and any of these diseases. For depression, our MR analysis indicated that excess adiposity was a risk factor (1.19 [1.11, 1.28]).

When comparing the MR analyses for FA and UFA there was no conclusive evidence (at $p<0.05$) of a non-metabolic or metabolic effect on depression, with both MR of UFA and FA directionally consistent with higher risk, but results were consistent with the null: higher FA (1.20 [0.98, 1.48] and higher UFA (1.02 [0.81, 1.30]) (**Figure 1g, Table 1**).

Integumentary System

Diseases in this category included psoriasis. MR analysis provided evidence for a causal association between higher BMI and higher odds of psoriasis (1.62 [1.20, 2.19]). Our MR analysis using body fat percentage as the exposure indicated that the risk was due to excess adiposity (1.78 [1.54, 2.05]).

When comparing the MR analyses for FA and UFA, our results suggested that the non-metabolic effect of higher adiposity is the predominant cause of the link between higher BMI and psoriasis. A 1-SD genetically-instrumented UFA was associated with a 2.11 [1.49, 2.99] higher odds of psoriasis and higher genetically-instrumented FA was associated with higher odds (1.20 [0.70, 2.06]) but this result was consistent with the null ($p>0.05$) (**Figure 1h, Table 1**).

Respiratory system

The diseases in this category included adult-onset asthma. MR analysis provided evidence for a causal association between higher BMI and higher odds of adult-onset asthma 1.25 [1.03, 1.52]. Our MR analysis using body fat percentage as the exposure indicated that the risk was due to excess adiposity (1.43 [1.25, 1.63]).

When comparing the MR analyses for FA and UFA, our results did not provide conclusive evidence for either a non-metabolic or metabolic effect. Whilst the MR analyses indicated the same direction of the effects of FA (1.14 [0.88, 1.49]) and UFA (1.34 [0.97, 1.87]) with higher odds of adult-onset asthma, these results included the null ($p < 0.05$) (**Figure 1i, Table 1**). Our results when using child-onset asthma are given in **Supplementary Figure 2c** and **Supplementary Table 5**.

Cancer

Diseases in this category included breast cancer, endometrial cancer, renal cancer, meningioma, prostate cancer, myeloma, pancreatic cancer, colorectal cancer, lung cancer, Barrett's oesophagus, ovarian cancer, and thyroid cancer. MR analysis provided evidence for a causal association between higher BMI and higher odds of endometrial (1.82 [1.26, 2.63]) and renal cancer (1.47 [1.12, 1.92]), and higher BMI and lower odds of breast cancer (0.60 [0.51, 0.70]). The MR evidence that excess adiposity was the predominant cause of the link between higher BMI and these three cancers was less clear than for other types of disease (**Figure 1j-l, Table 1**).

When comparing the MR analyses for FA and UFA our results did not provide consistent evidence for either a non-metabolic or a metabolic effect. We identified some evidence of a metabolic effect of higher adiposity with colorectal and ovarian cancer, with the MR of FA indicating lower odds of colorectal (0.67 [0.52, 0.85]) and ovarian (0.35 [0.18, 0.70]) cancers, but MR of UFA was consistent with the null ($p > 0.05$). For colorectal and ovarian cancer, our results were consistent when using sub-types of the conditions (**Supplementary Figure 2d-f, Supplementary Table 5**).

Sensitivity analyses

Out of a possible 82 total study-specific traits, weighted median MR results were directionally consistent with IVW analysis for 75 traits for BMI and 73 for body fat percentage, with 33 and 47 of these having $p < 0.05$ respectively. For FA and UFA, where sub-type colorectal cancer data was available, the total number of traits was 87, and 76 were directionally consistent for both exposures, with 22 and 39 having $p < 0.05$ respectively. Meanwhile, MR-Egger results were directionally consistent with IVW for 71 traits for BMI and 70 for body fat percentage, with 25 and 38 of these having $p < 0.05$ respectively. For FA and UFA, MR-Egger was directionally consistent for 60 and 67 traits, with 6 and 15 having $p < 0.05$ respectively (**Supplementary Table 5**). Of the 37 identified diseases, 31 were available in the UK Biobank, and the IVW analysis of these were directionally consistent with the FinnGen and/or published GWAS analysis for 28, 27, 24 and 27 traits for BMI, body fat percentage, FA and UFA, respectively (**Supplementary Table 6**). Of these, 18, 21, 9 and 16 had $p < 0.05$ respectively.

Discussion

We used a unique genetic approach to understand the role of higher adiposity uncoupled from its adverse metabolic effects in mechanisms linking obesity to higher risk of disease. We first used MR to provide evidence that higher BMI was causally associated with 21 diseases, broadly consistent with those from previous studies. For the majority (17) of these diseases, our results indicated that the BMI effect was predominantly due to excess adiposity rather than a non-fat mass component to BMI. We then used a more specific approach to test the separate roles of higher adiposity with and without its adverse metabolic effects.

Understanding the reasons why obesity leads to disease is important in order to better advise health professionals and patients of health risks linked to obesity, whether or not they show metabolic derangements. Many previous studies have used an MR approach to support a causal role of higher BMI in disease but few have attempted to investigate its separate components. This “uncoupling” of higher adiposity from its adverse metabolic effects is possible using specific genetic variants but has only been applied to individual conditions such as depression²³ and gastro-oesophageal reflux disease¹⁸. We discuss some of the more notable, and potentially clinically important, results below.

Cardio-metabolic diseases. We studied 3 groups of diseases that are often collectively labelled as “cardio-metabolic” - cardiovascular, including those affecting the peripheral vasculature; chronic kidney disease; and endocrine diseases such as type 2 diabetes. Previous studies, including those using MR, have shown that higher BMI leads to many of these diseases³⁴⁻³⁶, but our results provide

additional insight into the likely mechanisms. Our results showed clearly opposing effects of metabolically FA and UFA for coronary artery disease, peripheral artery disease, hypertension, stroke, type 2 diabetes and chronic kidney disease. These results are consistent with the well-established adverse metabolic effects of higher BMI on these diseases (contributing to atherosclerotic effects or linked to specific haemodynamic impacts)³⁷. For two further cardiovascular conditions, heart failure and atrial fibrillation, the results were less certain. For these two conditions, the evidence of a predominantly metabolic effect of higher BMI was very clear – with the MR of UFA consistent with effects at least as strong as those for coronary artery disease. However, in contrast to the results for coronary artery disease, the MR of FA was consistent with no effect. This comparison between the effects of FA and UFA may indicate that there is a partial mechanical as well as metabolic effect, perhaps mediated by excess weight of any type placing extra strain on the heart.

In contrast to the results for most of the cardiovascular diseases, our MR analyses provided strong evidence for a non-metabolic component mediating the effect of higher BMI on venous thromboembolism and deep vein thrombosis (two closely related conditions). This finding is clinically important as it suggests that treating metabolic risk factors associated with obesity without changing weight will not reduce the risk of deep vein thrombosis in individuals with obesity. Possible mechanisms could include higher intra-abdominal pressure (due to excess fat) and slower blood circulation in the lower limbs (due to a more sedentary lifestyle secondary to obesity, or mechanical occlusion of veins) promoting clot initiation and formation³⁸.

Musculoskeletal diseases. We observed clear differences for the role of higher BMI in different musculoskeletal diseases. For gout, opposing effects of FA and UFA clearly indicated a metabolic effect. Gout is a form of inflammatory arthritis caused by the deposition of urate crystals within the joints³⁹. Weight loss from bariatric surgery is associated with lower serum uric acid and lower risk of gout⁴⁰. A previous MR study showed overall obesity, but not the central location of fat, increased the risk of gout⁴¹. This result is in contrast with our finding of FA being protective against the risk of gout. The protective effect of FA could be due to improved insulin sensitivity leading to less insulin-enhanced reabsorption of organic anions such as urate⁴². In contrast to gout, our MR analysis provided strong evidence that a non-metabolic effect of higher adiposity is a cause of osteoarthritis and rheumatoid arthritis – with both FA and UFA leading to disease. For osteoarthritis, the effect of UFA was stronger than that of FA indicating both a metabolic and non-metabolic component. This is consistent with a causal association between higher adiposity and higher risk of osteoarthritis in non-weight bearing joints including hands⁴³. For rheumatoid arthritis, the effects of FA and UFA were similar, suggesting the non-metabolic, presumably load bearing, effect accentuating, or more readily unmasking, the autoimmune background risk, as the key BMI-related factor, although the confidence intervals were wider than those for osteoarthritis. For osteoporosis, we did not replicate the previous finding of a causal association between higher BMI and risk of osteoporosis (estimated by bone mineral density⁴⁴); however, we observed a causal association between higher body fat percentage and a higher risk of osteoporosis with consistent risk increasing effects of both FA and UFA. This finding adds to the complex relationship between higher BMI and osteoporosis, where higher BMI at earlier ages may increase bone accrual, but in later years results in adverse effects.

Gastrointestinal diseases. We observed differences in the effects of BMI when comparing the two gastrointestinal diseases, although the results are less conclusive than those for the musculoskeletal conditions. Here, our results were consistent with a predominantly non-metabolic effect mediating the association between higher BMI and higher risk of gallstones. Higher BMI has been shown to be causally associated with higher risk of gallstones⁴⁵. There are several possible mechanisms that could explain how higher BMI without its adverse metabolic effects could increase the risk of gallstones. These could include a sedentary lifestyle and gallbladder hypomotility secondary to increased abdominal fat mass⁴⁶. Metabolic mechanisms could include hepatic *de novo* cholesterol synthesis^{47,48}. For gastro-oesophageal reflux, the consistent direction and effect sizes of higher FA and UFA indicates a non-metabolic component, an effect that may be mechanical and better explained by higher central adiposity rather than overall BMI¹⁸.

Other diseases

For most of the other diseases tested it was difficult to draw firm conclusions about the role of metabolically FA and UFA. For some diseases, this was in part to the lack of MR evidence for a role of any form of higher BMI. For example, our MR analyses provided no evidence for the role of higher BMI in the neurodegenerative diseases Alzheimer's disease, multiple sclerosis and Parkinson's. These results are consistent with some but not all previous studies. For example, higher BMI is listed as a key risk factor for Alzheimer's disease⁴⁹, although with little evidence of causality, including MR studies that failed to show an effect^{50,51}. In contrast to our results,

recent MR studies have indicated that higher BMI is protective of Parkinson's disease¹⁴ and causally associated with higher risk of multiple sclerosis⁵². For the inflammatory skin disorder psoriasis, our results indicated that both higher BMI and higher body fat percentage are causally associated with higher risk but determining the underlying mechanism from the MR of FA and UFA was difficult. Higher BMI is a known cause of psoriasis^{9,53} and weight loss is a recommended treatment⁵³. It is possible that both metabolic and non-metabolic pathways are driving the risk. The non-metabolic pathways could include inflammation which is one of the possible mechanisms described to be causal^{54,55}. Further work is required to understand if psoriasis could be effectively treated by targeting the metabolic factors alone, or whether only weight loss will benefit such patients. For cancers, our results do not provide any clear additional insight into the likely mechanisms, with potentially stronger effects for BMI and UFA compared to body fat percentage in some analyses hard to explain biologically. The reasons why higher BMI is associated with cancers is uncertain, although several MR studies indicate that the association with many is causal^{56,57}, and that central adiposity may play a role⁵⁸. Exposure to higher insulin levels are a plausible mechanism and some studies have used MR to test insulin directly⁵⁹⁻⁶³. Our MR analysis reproduced the previous finding between higher adiposity and higher risk of endometrial⁶⁴ and renal cancer carcinoma⁶³, and lower risk of breast cancer^{13,60}. In contrast to previous MR studies showing a causal link between higher BMI and higher risk of prostate cancer^{65,66}, we identified a causal association between higher body fat percentage but lower risk of prostate cancer. The relationship between higher BMI and risk of breast cancer is complicated, with MR studies indicating that higher BMI is protective of post-menopausal breast cancer⁶⁷. This contrasts with the epidemiological associations but could be explained by effects of childhood BMI¹⁵.

Our study had a number of limitations. First, for some diseases, we may have not had sufficient power to detect an effect of BMI or to separate the effects, and this could explain some of the null findings, especially for conditions where we might have expected an effect, such as pulmonary embolism and aortic aneurysm, but there were smaller numbers of cases available. Second, the four genetic tests we used did not allow us to separate out further the different components to BMI. For example, metabolic effects could include multiple mechanisms or their combinations, including glycaemic, lipid related and inflammatory processes. Perhaps most importantly, the inflammatory profile of the FA variants needs further characterisation, given that it is associated with higher not lower hsCRP, as might have been expected given the link between metabolic and inflammatory effects⁶⁸. Likewise, effects of FA could be due to mechanical effects such as load bearing, lower activity levels, excess caloric consumption, or psychosocial, such as lower self-esteem. Further studies could use additional genetic variants to separate out effects in more detail. Third, in some situations it was harder to interpret the results from the MR FA and UFA analyses, especially when one appeared to show an effect and the other did not. One possibility is that some diseases are a combination of both non-metabolic and metabolic effects. Osteoarthritis was the best example of this potential scenario because both FA and UFA increased the risk of disease, but UFA to a greater extent. However, for other diseases, it could be hard to detect a combined effect because the MR with FA could be protective (if metabolic effects pre-dominate), increase risk (if non-metabolic effects pre-dominate) or null (if the two have similar effects). Finally, we used a p-value of 0.05 as a guide to discussing meaningful results and acknowledge that this is an arbitrary threshold and that we performed tests on 37 conditions. However, rather than correct for multiple tests, we noted that 74 of the 37 x 4 MR tests reached a p-value of <0.05 when we would only expect 8 by chance, suggesting many of the tests that did not reach a strict Bonferroni p<0.05 were meaningful.

In summary, we provided genetic evidence that the adverse metabolic consequences of higher BMI lead to coronary artery disease, peripheral artery disease, hypertension, stroke, heart failure, atrial fibrillation, type 2 diabetes, polycystic ovary syndrome, chronic kidney disease, colorectal and ovarian cancer, and gout, and the adverse non-metabolic consequences of higher BMI lead to osteoarthritis, rheumatoid arthritis, gastro-oesophageal reflux disease, cholelithiasis, depression, psoriasis and venous thromboembolism. These results emphasize that many people in the community who are of higher BMI are at risk of multiple chronic conditions that can severely impair their quality of life or cause morbidity or mortality, even if their metabolic parameters appear relatively normal.

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Competing interests:

The authors have declared that no competing interests exist except for Tim Frayling who has consulted for Boehringer Ingelheim and Sanofi and has a student supported by GSK.

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Table

Table 1. The inverse-variance weighted two-sample MR analysis/meta-analysis of 37 identified diseases from published GWAS and/or FinnGen for body mass index (BMI), body fat percentage, “favourable adiposity” (FA) and “unfavourable adiposity” (UFA) clusters. OR: odds ratio, 95% CI: 95% confidence interval; P: p-value.

			BMI			Body fat percentage			FA			UFA		
System	Disease	Study	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Cardiovascular	Abdominal aneurysm	Meta-analysis	1.16	(0.83, 1.62)	0.394	1.16	(0.91, 1.48)	0.233	0.81	(0.43, 1.51)	0.506	1.26	(0.71, 2.26)	0.430
Cardiovascular	Atrial fibrillation	Meta-analysis	1.65	(1.33, 2.05)	5.E-06	1.53	(1.21, 1.92)	3.E-04	0.79	(0.39, 1.61)	0.518	1.78	(1.50, 2.12)	6.E-11
Cardiovascular	Coronary artery disease	Meta-analysis	1.41	(1.10, 1.81)	0.007	1.39	(1.16, 1.68)	5.E-04	0.34	(0.25, 0.47)	2.E-11	1.66	(1.08, 2.54)	0.021
Cardiovascular	Deep vein thrombosis	FinnGen	1.68	(1.20, 2.37)	0.004	1.71	(1.40, 2.09)	2.E-07	3.45	(1.81, 6.57)	6.E-04	2.05	(1.15, 3.64)	0.020
Cardiovascular	Heart failure	Meta-analysis	1.86	(1.60, 2.16)	2.E-16	1.76	(1.65, 1.88)	2.E-67	0.85	(0.65, 1.11)	0.238	2.29	(1.85, 2.83)	2.E-14
Cardiovascular	Hypertension	FinnGen	2.18	(1.80, 2.64)	2.E-11	2.01	(1.79, 2.26)	6.E-29	0.34	(0.21, 0.55)	1.E-04	3.03	(2.18, 4.22)	2.E-07
Cardiovascular	Peripheral artery disease	FinnGen	1.87	(1.46, 2.39)	4.E-06	1.80	(1.52, 2.14)	4.E-11	0.20	(0.11, 0.38)	2.E-05	3.31	(2.09, 5.24)	1.E-05
Cardiovascular	Pulmonary embolism	FinnGen	1.23	(0.85, 1.78)	0.269	1.26	(1.02, 1.55)	0.032	2.40	(0.99, 5.84)	0.061	1.66	(0.94, 2.94)	0.090
Cardiovascular	Stroke	Meta-analysis	1.19	(1.07, 1.31)	1.E-03	1.23	(1.15, 1.31)	7.E-10	0.65	(0.52, 0.83)	4.E-04	1.43	(1.23, 1.67)	3.E-06
Cardiovascular	Venous thromboembolism	Meta-analysis	1.45	(1.27, 1.67)	8.E-08	1.57	(1.40, 1.77)	4.E-14	2.52	(1.82, 3.47)	2.E-08	1.63	(1.25, 2.13)	3.E-04
Endocrine	Polycystic ovary syndrome	Meta-analysis	4.11	(2.97, 5.70)	2.E-17	2.64	(2.11, 3.29)	1.E-17	0.51	(0.21, 1.23)	0.132	7.13	(3.66, 13.90)	8.E-09
Endocrine	Type 2 diabetes	Meta-analysis	2.97	(2.60, 3.39)	3.E-57	2.38	(2.12, 2.68)	5.E-49	0.11	(0.08, 0.16)	4.E-33	5.50	(4.29, 7.05)	4.E-41
Renal	Chronic kidney disease	Meta-analysis	1.21	(1.08, 1.36)	0.002	1.25	(0.98, 1.59)	0.071	0.64	(0.48, 0.84)	0.002	1.19	(0.97, 1.45)	0.092
Musculoskeletal	Gout	Meta-analysis	1.68	(1.42, 2.00)	3.E-09	1.66	(1.45, 1.89)	3.E-14	0.44	(0.29, 0.68)	2.E-04	2.49	(1.88, 3.29)	2.E-10
Musculoskeletal	Osteoarthritis	Meta-analysis	1.72	(1.37, 2.16)	2.E-06	1.82	(1.73, 1.91)	1.E-124	1.45	(1.19, 1.76)	2.E-04	2.20	(1.64, 2.95)	1.E-07
Musculoskeletal	Osteoporosis	Meta-analysis	1.04	(0.77, 1.40)	0.808	1.13	(1.03, 1.25)	0.010	1.13	(0.77, 1.64)	0.530	1.18	(1.01, 1.37)	0.034
Musculoskeletal	Rheumatoid arthritis	Meta-analysis	1.23	(1.04, 1.46)	0.017	1.49	(1.30, 1.70)	5.E-09	1.95	(1.24, 3.08)	0.004	1.61	(1.14, 2.27)	0.007
Gastrointestinal	Gallstones	FinnGen	1.87	(1.58, 2.23)	7.E-10	1.99	(1.78, 2.22)	1.E-30	1.37	(0.86, 2.19)	0.200	2.55	(1.88, 3.45)	9.E-07
Gastrointestinal	Gastro-oesophageal reflux disease	Meta-analysis	1.15	(1.05, 1.25)	0.002	1.48	(1.00, 2.18)	0.051	1.16	(0.96, 1.41)	0.119	1.26	(0.99, 1.61)	0.062
Nervous	Alzheimer's disease	Meta-analysis	0.98	(0.85, 1.13)	0.791	0.99	(0.96, 1.03)	0.697	1.00	(0.92, 1.08)	0.939	1.02	(0.98, 1.07)	0.335
Nervous	Depression	Meta-analysis	1.12	(0.98, 1.27)	0.092	1.19	(1.11, 1.28)	1.E-06	1.20	(0.98, 1.48)	0.074	1.02	(0.81, 1.30)	0.855
Nervous	Multiple sclerosis	FinnGen	0.81	(0.47, 1.40)	0.443	0.85	(0.58, 1.25)	0.407	1.53	(0.38, 6.20)	0.559	0.62	(0.24, 1.59)	0.332
Nervous	Parkinson's disease	Meta-analysis	0.96	(0.77, 1.19)	0.704	0.88	(0.63, 1.24)	0.472	1.35	(0.87, 2.08)	0.176	0.83	(0.44, 1.55)	0.551
Integumentary	Psoriasis	Meta-analysis	1.62	(1.20, 2.19)	0.001	1.78	(1.54, 2.05)	3.E-15	1.20	(0.70, 2.06)	0.514	2.11	(1.49, 2.99)	3.E-05
Respiratory	Adult-onset asthma	Meta-analysis	1.25	(1.03, 1.52)	0.022	1.43	(1.25, 1.63)	3.E-07	1.14	(0.88, 1.49)	0.319	1.34	(0.97, 1.87)	0.080
Cancer	Barrett's oesophagus	FinnGen	1.29	(0.55, 3.02)	0.558	1.42	(0.79, 2.54)	0.242	3.16	(0.39, 25.47)	0.288	0.62	(0.14, 2.65)	0.522
Cancer	Breast cancer	Meta-analysis	0.60	(0.51, 0.70)	4.E-10	0.84	(0.71, 0.98)	0.032	1.12	(0.64, 1.94)	0.689	0.52	(0.39, 0.68)	4.E-06
Cancer	Cancer myeloma	FinnGen	1.60	(0.76, 3.40)	0.221	1.43	(0.85, 2.39)	0.179	1.96	(0.25, 15.59)	0.529	1.33	(0.30, 5.99)	0.710
Cancer	Colorectal cancer	Meta-analysis	1.09	(0.89, 1.35)	0.408	0.96	(0.77, 1.19)	0.697	0.67	(0.52, 0.85)	0.001	1.20	(0.97, 1.50)	0.094
Cancer	Endometrial cancer	Meta-analysis	1.82	(1.26, 2.63)	0.002	1.36	(0.86, 2.16)	0.190	0.93	(0.53, 1.63)	0.802	1.48	(0.44, 4.98)	0.527
Cancer	Lung cancer	FinnGen	1.21	(0.75, 1.96)	0.444	1.33	(1.00, 1.77)	0.051	0.64	(0.23, 1.78)	0.401	1.36	(0.65, 2.84)	0.426
Cancer	Meningioma	FinnGen	0.62	(0.36, 1.06)	0.085	1.01	(0.71, 1.43)	0.967	1.06	(0.31, 3.61)	0.928	0.36	(0.15, 0.86)	0.028
Cancer	Ovarian cancer	Meta-analysis	1.15	(0.72, 1.85)	0.562	1.16	(0.69, 1.93)	0.579	0.35	(0.18, 0.70)	0.003	1.26	(0.80, 1.99)	0.315
Cancer	Pancreatic cancer	FinnGen	1.39	(0.67, 2.88)	0.376	1.25	(0.79, 1.97)	0.345	3.30	(0.50, 21.83)	0.224	1.45	(0.45, 4.61)	0.536
Cancer	Prostate cancer	Meta-analysis	0.91	(0.81, 1.03)	0.135	0.90	(0.83, 0.97)	0.006	0.97	(0.79, 1.19)	0.772	0.94	(0.77, 1.15)	0.565

Cancer	Renal cancer	Meta-analysis	1.47	(1.12, 1.92)	0.005	1.23	(0.94, 1.60)	0.126	0.94	(0.33, 2.72)	0.910	1.72	(1.18, 2.51)	0.005
Cancer	Thyroid cancer	FinnGen	0.90	(0.52, 1.56)	0.719	0.73	(0.51, 1.06)	0.103	0.91	(0.24, 3.40)	0.888	1.09	(0.42, 2.86)	0.859

Figures

Figure 1

The inverse-variance weighted (IVW) two-sample MR analysis/meta-analysis of published GWAS and/or FinnGen for body mass index (BMI), body fat percentage, “favourable adiposity” (FA) and “unfavourable adiposity” (UFA) clusters for disease outcomes grouped into (a-b) cardiovascular system; (c) endocrine system; (d) renal system; (e) musculoskeletal system; (f) gastrointestinal system; (g) nervous system; (h) integumentary system; (i) respiratory system; and (j-l) cancer. The error bars represent the 95% confidence intervals of the IVW estimates in odds ratio per standard deviation change in genetically determined BMI, body fat percentage, FA and UFA.

Supplementary Files

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