Epidemiology and Global Health

A Sex-specific Mendelian Randomization-Phenome-Wide Association Study of Body Mass Index

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eLife Assessment

The study presents some **useful** findings on Mendelian randomization-phenome-wide association, with BMI associated with health outcomes, and there is a focus on sex differences. Although there are some **solid** phenotype and genotype data, some of the data are **incomplete** and could be better presented, perhaps benefiting from more rigorous approaches. Confirmation and further assessment of the observed sex differences will add further value.

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Abstract

Background

Trials of incretins are making it increasingly clear that body mass index (BMI) is linked to several diseases throughout life, but trials cannot provide a comprehensive assessment of the role of BMI in health-related attributes for men and women. To systematically investigate the role of BMI, we conducted a sex-specific Mendelian randomization-phenome-wide association study.

Methods

We comprehensively examined the associations of genetically predicted BMI in women (n: 194,174) and men (n: 167,020) with health-related attributes from the UK Biobank with inverse variance weighting and sensitivity analysis.

Results

BMI impacted 232 of 776 traits considered in women and 204 of 681 traits in men, after adjusting for false discovery; differences by sex were found for 105 traits. BMI was more strongly positively associated with heart disease, heart failure and hypertensive heart disease in men than women. BMI was more strongly positively associated with apolipoprotein B (ApoB), diastolic blood pressure, neuroticism, arthritis and triglycerides in women than men.

Conclusion

Our study revealed that BMI might affect a wide range of health-related attributes and highlights notable sex differences in its impact, including opposite associations for certain attributes, such as ApoB and neuroticism. These findings emphasize the importance of maintaining a healthy BMI.

Funding

None

Impact statement

BMI may affect a wide range of health-related attributes and there are notable sex differences in its impact, including opposite associations for certain attributes, such as ApoB and neuroticism. These findings emphasize the importance of maintaining a healthy BMI.

Introduction

Global obesity prevalence more than doubled from 1980 to 2008 (Finucane et al., 2011). In 2022, one in eight people were obese worldwide (WHO, 2024). Body mass index (BMI) is a longstanding measure of obesity, despite its high specificity but low sensitivity (Chooi et al., 2019; Okorodudu et al., 2010). Many observational studies have found BMI associated with disease risk factors and lifespan (Collaboration, 2009; Kahn et al., 2006; Khan et al., 2018), generally, a higher BMI is detrimental to health. However, BMI does not account well for fat distribution. For men and women with the same BMI, women tend to store more fat (Power & Schulkin, 2008). Furthermore, men tend to store fat around their organs, while women are more likely to store it subcutaneously (Power & Schulkin, 2008), potentially leading to different health impacts by sex (Costanzo et al., 2022; Power & Schulkin, 2008). As such, the effect of BMI on health may vary between men and women and may be a modifiable factor contributing to differences in lifespan by sex.

Few previous observational studies have systematically assessed the role of BMI in health and disease, and are limited by their susceptibility to confounding (Davey Smith & Ebrahim, 2003). Mendelian randomization (MR) studies reduce confounding by using genetic proxies, such as single nucleotide polymorphisms (SNPs), for exposures. Previous phenome-wide association studies using MR (MR-PheWASs) have identified impacts of BMI on endocrine disorders,

circulatory diseases, inflammatory and dermatological conditions, and some biomarkers (Hyppönen et al., 2019; Millard et al., 2015), but were conducted before the advent of large-scale genome-wide association studies (GWASs) and were not sex-specific. Previous MR studies and recent trials of incretins have expanded our knowledge about a broad range of effects of BMI (Larsson et al., 2020; Marso et al., 2016). To our knowledge, no sex-specific PheWAS has investigated the effects of BMI on health outcomes. To address this gap, we conducted a sex-specific PheWAS, utilizing the largest available sex-specific GWAS, to explore the impact of BMI on health-related attributes.

Methods

Data sources

Exposure: Body mass index

To obtain genetic information for BMI (inverse rank normalized) sex-specifically, we used BMI from two sources, the UK Biobank, a prospective cohort study of half a million adults, and the Genetic Investigation of ANthropometric Traits (GIANT) consortium (Locke et al., 2015), a GWAS meta-analysis of 339,224 participants mostly of European ancestry. The UK Biobank has the advantage of a larger sample size and denser genotyping but is the only large-scale sex-specific source for many outcomes. The sex-specific UK Biobank BMI GWAS conducted by Neale Lab (women: 194,174; men: 167,020) was adjusted for age, age squared and the first 20 principal components (*https://www.nealelab.is/uk-biobank/faq*). The GIANT GWAS has the advantage of using a different sample from the UK Biobank but is smaller with less dense genotyping (women: 171,977; men: 152,893). The sex-specific GIANT GWAS was adjusted for age, age squared, and study-specific covariates (Locke et al., 2015). We also considered overall BMI from the GIANT (n: 681,275) which includes the UK Biobank participants (approximately 64%), and was adjusted for age, age squared, principal components and study-specific covariates (Yengo et al., 2018).

Outcomes

The UK Biobank is currently the largest and most comprehensive source for sex-specific GWAS, provided by Neale Lab (women: 194,174; men: 167,020), including many disease outcomes and physiological attributes. The average age at recruitment of UK Biobank participants was 57 years, as described previously (Collins, 2012).

Outcomes: Inclusion and exclusion criteria

For continuous outcomes only rank normalized health attributes with at least 1,000 participants (Verma et al., 2018) were included to maintain statistical power. For binary attributes only those with at least 200 cases were included; duplicated phenotypes were excluded. We further excluded very similar attributes. Where an attribute has a standard measure, such as forced expiratory volume in 1 second, we used that in preference to similar measures. We also excluded attributes only assessed in selected subgroups of the UK Biobank participants, such as an electrocardiogram, which was only conducted in healthy people (Ramírez et al., 2021). Some attributes were available from both self-report and doctor diagnosis, in which case we used self-report because of the higher case number and hence greater statistical power. Finally, attributes with known measurement issues, such as estrogen and immature reticulocyte fraction, were excluded (Newman & Handelsman, 2014; Piva et al., 2015). Detailed exclusion criteria are listed in **Figure 1**.

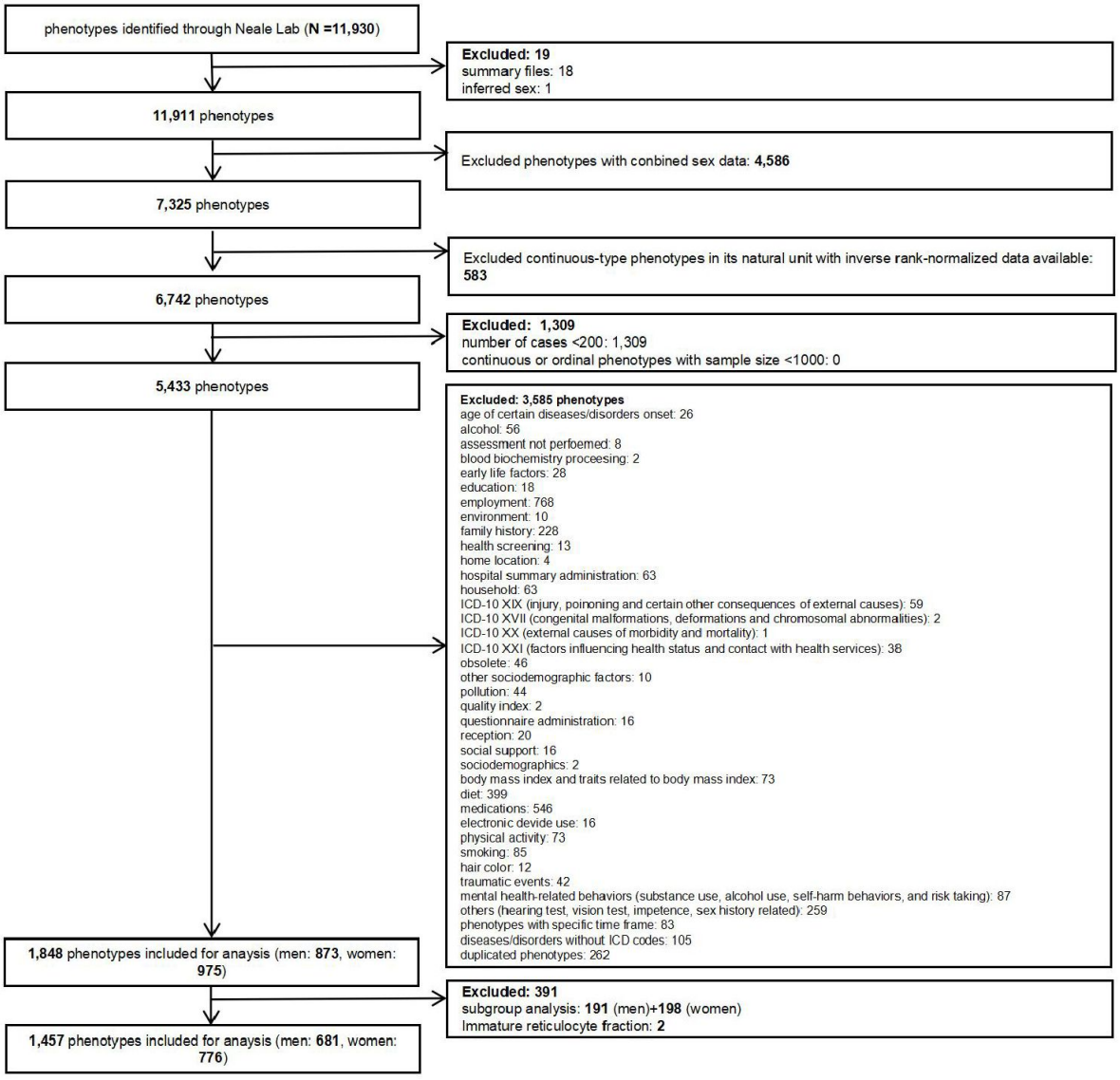

Figure 1.

Selection criteria for the health-related attributes

Outcomes: Attribute categorization

We categorized attributes as age at recruitment, physical measures, lifestyle and environmental, medical conditions, operations, physiological factors, cognitive function, health and medical history, sex-specific factors, blood assays and urine assays, as recommended by the UK Biobank. Binary attributes with an International Classification of Diseases-10 code were categorized by International Classification of Diseases-10 chapter, as (I) infectious diseases, (II) neoplasms, (III) diseases of the hematopoietic system and blood disorders, (IV) endocrine and metabolic diseases, (V) psychological disorders, (VI) diseases of the nervous system, (VII and VIII) diseases of the sensory system (eyes and ears), (IX) diseases of the circulatory system, (X) diseases of the respiratory system, (XI) diseases of the digestive system, (XII) diseases of skin and subcutaneous tissue, (XIII) diseases of the musculoskeletal system and connective tissue, (XIV) diseases of the genitourinary system, (XV) pregnancy, childbirth, and the puerperium, and (XVIII) symptoms.

Statistical analysis

MR was used to assess sex-specific effects of genetically predicted BMI on each attribute considered. Specifically, inverse-variance weighted estimates were used initially, i.e., meta-analysis of Wald estimates (SNP on outcome divided by SNP on exposure), and then sensitivity analysis (MR-Egger) was used for any associations found. The significance level was adjusted for the false discovery rate to account for multiple comparisons (Benjamini & Hochberg, 1995). Specifically, we ranked the p-values for men and women respectively, calculated the Benjamini-Hochberg (BH) value, and identified the significant attributes influenced by BMI using the BH value. We used a z-test to evaluate differences by sex (Altman & Bland, 2003). We used the R packages "TwoSampleMR" (version: 0.6.1), "Mendelian Randomization" (version: 0.10.0) and "metafor" (version: 4.6-0) to assess sex-differences.

Results

Initial analysis using sex-specific BMI from the GIANT yielded similar estimates to using sex-specific BMI from the UK Biobank but had fewer single nucleotide polymorphisms resulting in wider confidence intervals (S Table 1 and S Table 2). We presented the results obtained using sex-specific BMI from the UK Biobank.

Sex-specific estimates

In men, BMI was associated with 204 of the 681 health-related attributes considered using the false discovery rate (**Figure 2**, S Table 3). As expected, BMI was positively associated with heart disease, heart failure, hypertensive heart disease, diabetes, hypertension, sleep apnoea, daytime dozing, triglycerides, urinary potassium, urinary sodium and major surgeries. BMI was also inversely associated with age at recruitment, osteoporosis, hay fever, high density lipoprotein cholesterol (HDL-c), cholesterol, low density lipoprotein (LDL), sex hormone binding globulin (SHBG) and total testosterone. Positive associations of BMI with higher risk of digestive system cancers, lymphomas, primary lymphoid and hematopoietic malignancies, and esophageal cancer were also found in men. Furthermore, we found higher BMI associated with accelerated facial aging and baldness.

In women, BMI was associated with 232 of 776 attributes considered using the false discovery rate (**Figure 3**, S Table 3). As expected, BMI was positively associated with heart disease, heart failure, hypertensive heart disease, diabetes, hypertension, sleep apnoea, daytime dozing, apolipoprotein B (ApoB), triglycerides, total testosterone and urinary potassium and sodium and major surgeries. BMI was also inversely associated with osteoporosis, HDL-c, cholesterol, LDL and

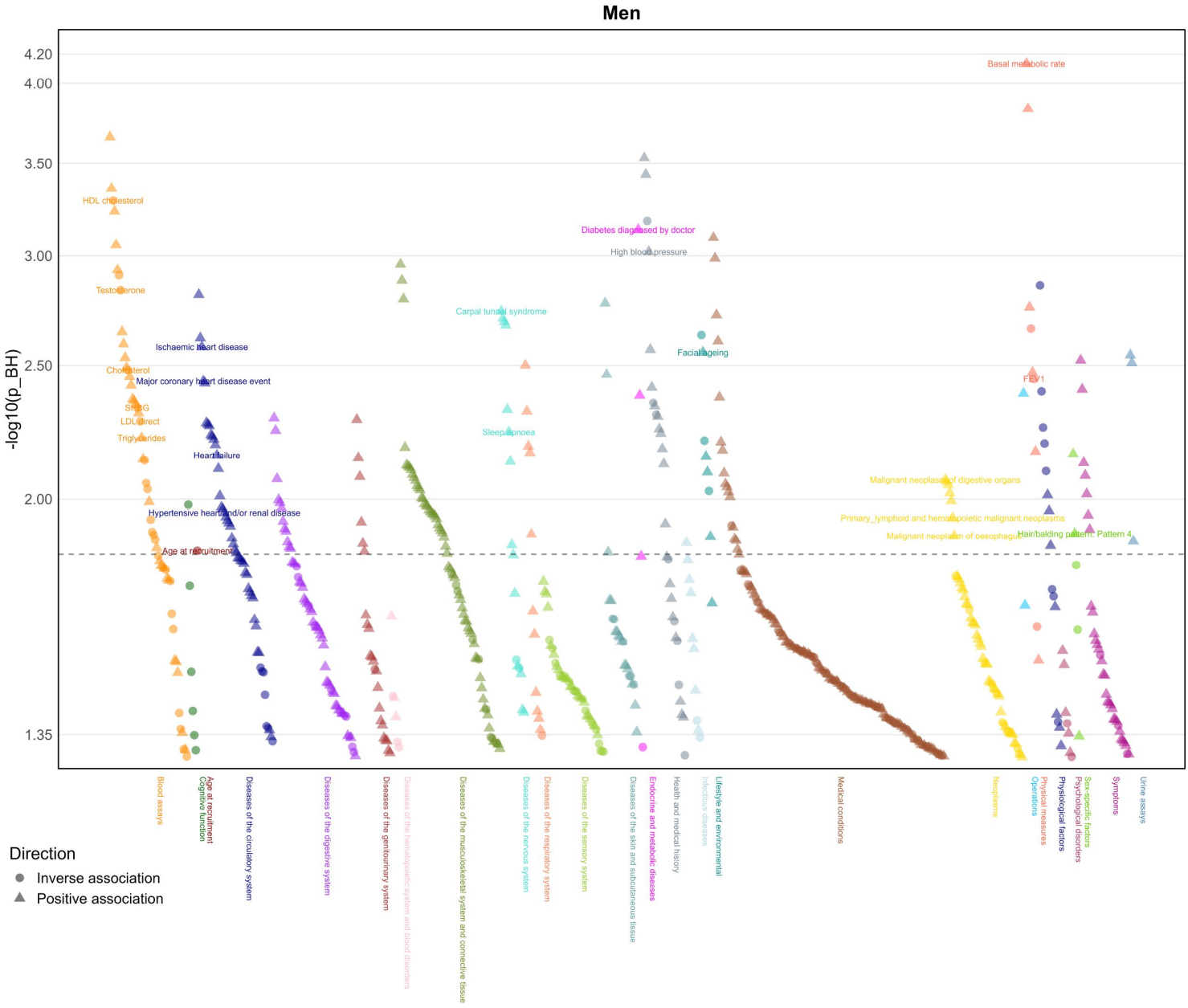

Figure 2.

Manhattan plot of body mass index on health-related attributes in men (n: 167,020) from the UK Biobank

SHBG. BMI was positively associated with risk of uterine cancer, cancer of the bronchus and lung and intrathoracic organs, as well as cancers affecting the skin and female reproductive organs. Higher BMI in women was also associated with accelerated facial aging.

Differences by sex

We found significant differences by sex in the associations of BMI with 105 health-related attributes. Most differences (74) were in magnitude but not direction, directionally different associations were found for 31 attributes. BMI was inversely associated with ApoB, psoriatic arthropathy, iron deficiency anemia, hernia, hand grip strength and total testosterone in men, while positively associated with these traits in women (**Figure 4**). BMI was positively associated with the risk of malignant neoplasm of the urinary tract and colon in men but was inversely associated in women. BMI was positively associated with hernia, cervicalgia, mononeuropathies of lower limb and degeneration of macula and posterior pole in women, whilst inversely associated in men. BMI was inversely associated with anemias in men, but positively associated in women. BMI was inversely associated with neuroticism scores, sensitivity to hurt feelings, and frequency of seeking of medical advice for nerves, anxiety, tension, or depression in men. However, BMI was positively with neuroticism scores and seeking medical advice for these issues in women.

Several notable differences in magnitude by sex were also found. BMI was more strongly and inversely associated with osteoporosis SHBG, albumin and bilirubin in women than in men. BMI was more strongly and inversely associated with LDL and hay fever in men than women. BMI was more strongly and positively associated with diastolic blood pressure, depression, arthritis, triglycerides and hypothyroidism in women than men. BMI was more strongly and positively associated with heart disease, heart failure, hypertensive heart disease, lymphomas, facial aging, and sleep apnoea in men than women.

Discussion

Consistent with previous studies BMI was positively associated with many health-related attributes, such as heart disease, heart failure, hypertensive heart disease, diabetes, hypertension and sleep apnoea. Our study adds by showing sex-differences in some traits related to cancer and psychological disorders as well as ApoB and showing stronger associations in men than women for common cardiovascular diseases.

Comparison with previous studies

Consistent with previous MR studies, BMI was positively associated with the risk of heart disease, heart failure, hypertensive heart disease (Riaz et al., 2018), hypertension (Riaz et al., 2018) and diabetes (Larsson & Burgess, 2021) in both men and women as would be expected. We also found BMI was inversely associated with osteoporosis (Larsson & Burgess, 2021), with a stronger association in women than men. A previous MR study found height and fat-free mass positively associated with follicular lymphoma (Zhou et al., 2024), however, we found BMI positively associated with lymphomas in men, but not women (although directionally consistent but not significant after considering multiple comparisons). Another MR study found BMI positively associated with asthma and poorer lung function, but not with hay fever (Skaaby et al., 2018), when we found BMI inversely associated with hay fever in men, but not in women. Previous studies have shown BMI inversely associated with Na/K (Zanetti et al., 2020), while we found BMI positively associated with urinary potassium and sodium. Additionally, we found a positive association of BMI with major surgeries. Consistent with the previous MR study (Ardissino et al., 2022), we also found BMI positively associated with sleep apnoea we also found positive associations with daytime dozing in both sexes, which may indicate effects of BMI on quality of life. Higher BMI was associated with a younger age at recruitment among men, suggesting poorer

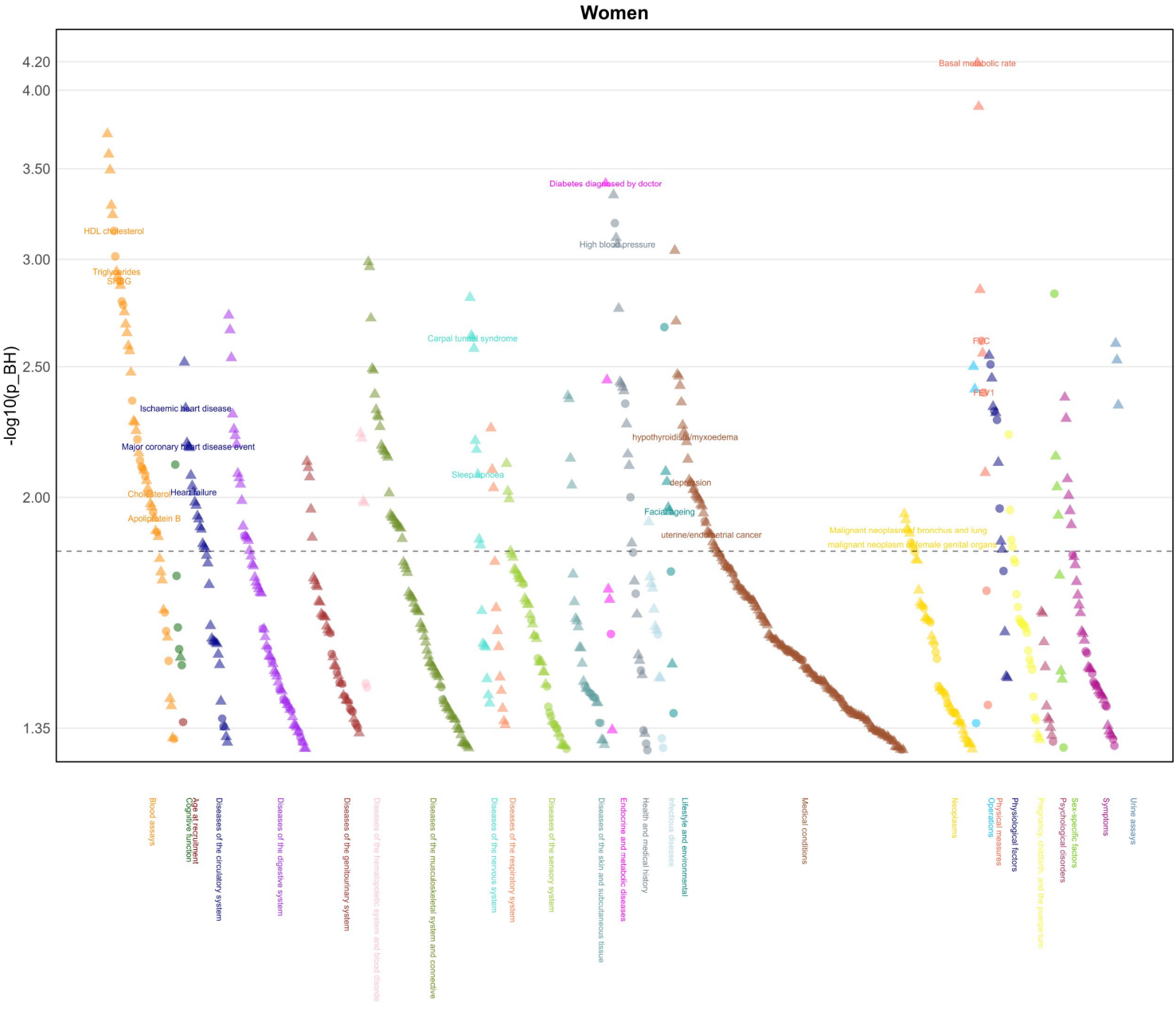

Figure 3.

Manhattan plot of body mass index on health-related attributes in women (n: 194,174) from the UK Biobank

ealth-related traits	Category	Men	Women	Directionally discord between sexes	Absolute estimations
HBG	Blood assays	Inverse	Inverse	No	Greater absolute estimations in women
lbumin	Blood assays	Inverse	Inverse	No	Greater absolute estimations in women
itamin D	Blood assays	Inverse	Inverse	No	Greater absolute estimations in women
holesterol	Blood assays	Inverse	Inverse	No	Greater absolute estimations in men
otal bilirubin	Blood assays	Inverse	Inverse	No	Greater absolute estimations in women
DL direct	Blood assays	Inverse	Inverse	No	Greater absolute estimations in men
irect bilirubin	Blood assays	Inverse	Inverse	No	Greater absolute estimations in women
latelet count	Blood assays	Inverse	Positive	Yes	Greater absolute estimations in men
estosterone	Blood assays	Inverse	Positive	Yes	Greater absolute estimations in men
poliprotein B	Blood assays	Inverse	Positive	Yes	Greater absolute estimations in women
latelet crit	Blood assays	Inverse	Positive	Yes	Greater absolute estimations in women
spartate aminotransferase	Blood assays	Positive	Positive	No	Greater absolute estimations in men
lkaline phosphatase	Blood assays	Positive	Positive	No	Greater absolute estimations in women
eutrophil count	Blood assays	Positive	Positive	No	Greater absolute estimations in women
ed blood cell (erythrocyte) distribution width	Blood assays	Positive	Positive	No	Greater absolute estimations in women
riglycerides	Blood assays	Positive	Positive	No	Greater absolute estimations in women
rate	Blood assays	Positive	Positive	No	Greater absolute estimations in women
-reactive protein	Blood assays	Positive	Positive	No	Greater absolute estimations in women
iagnoses - main ICD10: I35 Nonrheumatic aortic valve disorders	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
eripheral artery disease	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
eath due to cardiac causes	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
eart failure,strict	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
iagnoses - main ICD10: I26 Pulmonary embolism	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
VT of lower extremities and pulmonary embolism	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
enous thromboembolism	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
yocardial infarction, strict	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
ajor coronary heart disease event	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
ajor coronary heart disease event excluding revascularizations	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
oronary atherosclerosis	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
chaemic heart disease, wide definition	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
iseases of the circulatory system	Diseases of the circulatory system	Positive	Positive	No	Greater absolute estimations in men
iagnoses - main ICD10: K60 Fissure and fistula of anal and rectal regions	Diseases of the digestive system	Positive	Positive	No	Greater absolute estimations in men
iagnoses - main ICD10: K81 Cholecystitis	Diseases of the digestive system	Positive	Positive	No	Greater absolute estimations in women
ernia	Diseases of the digestive system	Inverse	Positive	Yes	Greater absolute estimations in women
iagnoses - main ICD10: K80 Cholelithiasis	Diseases of the digestive system	Positive	Positive	No	Greater absolute estimations in women
isorders of gallbladder, biliary tract and pancreas	Diseases of the digestive system	Positive	Positive	No	Greater absolute estimations in women
iseases of the digestive system	Diseases of the digestive system	Positive	Positive	No	Greater absolute estimations in women
iagnoses - main ICD10: N17 Acute renal failure	Diseases of the genitourinary system	Positive	Positive	No	Greater absolute estimations in men
iagnoses - main ICD10: N39 Other disorders of urinary system	Diseases of the genitourinary system	Positive	Positive	No	Greater absolute estimations in women
ther anaemias	Diseases of the hematopoietic system and blood disorders	Inverse	Positive	Yes	Greater absolute estimations in women
ther and unspecified anaemias	Diseases of the hematopoietic system and blood disorders	Inverse	Positive	Yes	Greater absolute estimations in women
on deficiency anaemia	Diseases of the hematopoietic system and blood disorders	Inverse	Positive	Yes	Greater absolute estimations in women
iseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	Diseases of the hematopoietic system and blood disorders	Positive	Positive	No	Greater absolute estimations in women
ervicalgia	Diseases of the musculoskeletal system and connective tissue	Inverse	Positive	Yes	Greater absolute estimations in women
oft tissue disorders related to use, overuse and pressure	Diseases of the musculoskeletal system and connective tissue	Positive	Positive	No	Greater absolute estimations in men
pingement syndrome of shoulder	Diseases of the musculoskeletal system and connective tissue	Positive	Positive	No	Greater absolute estimations in women
ain in limb	Diseases of the musculoskeletal system and connective tissue	Positive	Positive	No	Greater absolute estimations in women
ther soft tissue disorders, not elsewhere classified	Diseases of the musculoskeletal system and connective tissue	Positive	Positive	No	Greater absolute estimations in women
iagnoses - main ICD10: M79 Other soft tissue disorders, not elsewhere classified	Diseases of the musculoskeletal system and connective tissue	Positive	Positive	No	Greater absolute estimations in women
iagnoses - main ICD10: G57 Mononeuropathies of lower limb	Diseases of the nervous system	Inverse	Positive	Yes	Greater absolute estimations in women
leep apnoea	Diseases of the nervous system	Positive	Positive	No	Greater absolute estimations in men
iagnoses - main ICD10: G47 Sleep disorders	Diseases of the nervous system	Positive	Positive	No	Greater absolute estimations in men
arpal tunnel syndrome	Diseases of the nervous system	Positive	Positive	No	Greater absolute estimations in women
erve, nerve root and plexus disorders	Diseases of the nervous system	Positive	Positive	No	Greater absolute estimations in women
iagnoses - main ICD10: J18 Pneumonia, organism unspecified	Diseases of the respiratory system	Positive	Positive	No	Greater absolute estimations in men
iseases of the respiratory system	Diseases of the respiratory system	Positive	Positive	No	Greater absolute estimations in men
iagnoses - main ICD10: H61 Other disorders of external ear	Diseases of the sensory system	Positive	Inverse	Yes	Greater absolute estimations in men
egeneration of macula and posterior pole	Diseases of the sensory system	Inverse	Positive	Yes	Greater absolute estimations in women
iagnoses - main ICD10: L03 Cellulitis	Diseases of the skin and subcutaneous tissue	Positive	Positive	No	Greater absolute estimations in men
iabetes diagnosed by doctor	Endocrine and metabolic diseases	Positive	Positive	No	Greater absolute estimations in men
lood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor: Hayfever, allergic rhinitis or eczema	Health and medical history	Inverse	Inverse	No	Greater absolute estimations in men
lood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor: None of the above	Health and medical history	Positive	Inverse	Yes	Greater absolute estimations in women
ascular/heart problems diagnosed by doctor: Heart attack	Health and medical history	Positive	Positive	No	Greater absolute estimations in men
hest pain or discomfort	Health and medical history	Positive	Positive	No	Greater absolute estimations in women
outh/teeth dental problems: Dentures	Health and medical history	Positive	Positive	No	Greater absolute estimations in women
orning/evening person (chronotype)	Lifestyle and environmental	Inverse	Inverse	No	Greater absolute estimations in men
acial ageing	Lifestyle and environmental	Positive	Positive	No	Greater absolute estimations in men
on-cancer illness code, self-reported: osteoporosis	Medical conditions	Inverse	Inverse	No	Greater absolute estimations in women
on-cancer illness code, self-reported: headaches (not migraine)	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in men
on-cancer illness code, self-reported: pernicious anaemia	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in women
on-cancer illness code, self-reported: psoriatic arthropathy	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in women
on-cancer illness code, self-reported: eye/eyelid problem	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in men
on-cancer illness code, self-reported: allergy/hypersensitivity/anaphylaxis	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in women
on-cancer illness code, self-reported: ulcerative colitis	Medical conditions	Positive	Inverse	Yes	Greater absolute estimations in men
on-cancer illness code, self-reported: bladder problem (not cancer)	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in women
on-cancer illness code, self-reported: helicobacter pylori	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: muscle or soft tissue injuries	Medical conditions	Positive	Inverse	Yes	Greater absolute estimations in men
on-cancer illness code, self-reported: muscle/soft tissue problem	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in women
on-cancer illness code, self-reported: gout	Medical conditions	Positive	Positive	No	Greater absolute estimations in men
on-cancer illness code, self-reported: cervical spondylosis	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: arthritis (nos)	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: unclassifiable	Medical conditions	Inverse	Positive	Yes	Greater absolute estimations in women
on-cancer illness code, self-reported: cholelithiasis/gall stones	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: depression	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: hypothyroidism/myxoedema	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: gastro-oesophageal reflux (gord) / gastric reflux	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: angina	Medical conditions	Positive	Positive	No	Greater absolute estimations in men
on-cancer illness code, self-reported: asthma	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
on-cancer illness code, self-reported: osteoarthritis	Medical conditions	Positive	Positive	No	Greater absolute estimations in women
alignant neoplasm of urinary organs	Neoplasms	Positive	Inverse	Yes	Greater absolute estimations in men
iagnoses - main ICD10: D35 Benign neoplasm of other and unspecified endocrine glands	Neoplasms	Positive	Positive	No	Greater absolute estimations in women
alignant neoplasm of colon	Neoplasms	Positive	Inverse	Yes	Greater absolute estimations in men
mphomas	Neoplasms	Positive	Positive	No	Greater absolute estimations in men
alignant neoplasm of digestive organs	Neoplasms	Positive	Positive	No	Greater absolute estimations in men
and grip strength (right)	Physical measures	Positive	Inverse	Yes	Greater absolute estimations in women
iastolic blood pressure, automated reading	Physical measures	Positive	Positive	No	Greater absolute estimations in women
nsitivity / hurt feelings	Physiological factors	Inverse	Positive	Yes	Greater absolute estimations in women
euroticism score	Physiological factors	Inverse	Positive	Yes	Greater absolute estimations in men
een doctor (GP) for nerves, anxiety, tension or depression	Physiological factors	Inverse	Positive	Yes	Greater absolute estimations in women
iserableness	Physiological factors	Positive	Positive	No	Greater absolute estimations in women
neliness, isolation	Physiological factors	Positive	Positive	No	Greater absolute estimations in women
ed-up feelings	Physiological factors	Positive	Positive	No	Greater absolute estimations in women
iagnoses - main ICD10: R04 Haemorrhage from respiratory passages	Symptoms	Positive	Inverse	Yes	Greater absolute estimations in men
iagnoses - main ICD10: R31 Unspecified haematuria	Symptoms	Positive	Inverse	Yes	Greater absolute estimations in men
otassium in urine	Urine assays	Positive	Positive	No	Greater absolute estimations in women

Figure 4.

Sex differences of body mass index on health-related attributes in men (n: 167,020) and women (n: 194,174)

survival to recruitment in men given the GWAS adjusted for age and the short recruitment window makes period effects unlikely. However, the association was less evident in women, with no sex difference. Notably, higher BMI may be more detrimental to lifespan in men than women, especially at younger ages (Fontaine et al., 2003).

Differences in the associations of body mass index with health-related attributes in men and women

BMI was more strongly associated with heart disease in men than women. BMI was positively associated with ApoB in women, whereas in men, the association was inverse (but not significant after correction for multiple comparisons); however, the sex difference was significant. This pattern contrasts with earlier MR studies that reported an inverse association of BMI with ApoB in the general population (Bell et al., 2022). BMI being more strongly associated with heart disease in men than women while also being protective for the key heart disease risk factor of ApoB requires some explanation. BMI is a complex phenotype that may represent different attributes or have different consequences in men and women. Fat mass storage tends to differ between men and women (visceral versus subcutaneous) (Power & Schulkin, 2008). The causes of BMI may also differ between men and women, due to occupational roles, gender-based food preferences or cultural norms (Kanter & Caballero, 2012). Alternatively, unknown factors affected by BMI could contribute to heart disease specifically to men. In terms of psychological disorders, women being more affected psychologically by higher BMI is consistent with sociocultural pressures and norms surrounding women's rather than men's bodies (Esnaola et al., 2010; Schwartz & Brownell, 2004). We also found that BMI was associated with balding in men but not in women. Moreover, BMI was positively associated with facial aging in both men and women, with larger effects in men.

Strengths and limitations

A major strength of this study was the focus on sex differences, which have not been explicitly explored in previous PheWAS of BMI, despite differences in lifespan by sex Despite the large sample size and the broad range of outcomes considered in this study, limitations and concerns exist. First, MR has stringent assumptions, i.e., relevance, independence and exclusion restriction. The F-statistics were above 10, which addresses relevance. MR is largely free from confounding by design. For a few attributes (37 out of 1,457), the MR-Egger intercept was significant while the IVW estimate was not (S Table 4), potentially indicating horizontal pleiotropic effects or the play of chance, which requires further investigation. Second, MR assesses BMI lifetime effects of BMI, which may differ from those of short-term weight changes or weight cycling. Third, not all attributes were included. For example, heart rate from ECG and age at asthma diagnosis were excluded, because such information was limited to selected subgroups. Fourth, given the study's exploratory nature, we allowed for multiple comparisons to minimize chance findings, which means some BMI effects may not be captured. However, such comprehensive consideration may identify previously unknown or ignored impacts, such as facial aging and balding. Fifth, while the UK Biobank does not fully represent the UK population, representativeness is not crucial for causal inference, as long as the sample is not selected on exposure and outcome (Greenland, 2003). Sixth, focusing on a European population may limit generalizability, but helps reduce bias from population stratification. Seventh, we excluded replicated or very similar attributes, potentially missing some attributes. However, this reduces false negatives when adjusting for multiple comparisons. Eighth, this study is open to selection bias because genetic endowment is lifelong but the UK Biobank participants are middle-aged or older, so potential recruits who did not live to recruitment because of their BMI are missing, which may bias estimates towards the null or inverse for harmful binary outcomes (Thompson et al., 2013), but less likely affects continuous outcomes (Smit et al., 2019). Ninth, we focused on BMI, because it is well accepted and easy to measure, although waist-to-hip ratio may be a better marker for mortality. Tenth, although this study primarily utilized sex-specific BMI, we also conducted analyses using overall BMI from GIANT including the UK Biobank, which gave a generally similar interpretation (S Table

5). Using a sex-specific BMI may lead to lower statistical power than using overall population BMI, but allows for the detection of traits that are affected differently by BMI by sex. Including findings from the overall population BMI makes the results more comparable to previous similar studies. Eleventh, our study did not find associations of BMI with some early-onset cancers possibly because early-onset cancers tend to be of germline origin (Qing et al., 2020). Twelfth, we used information from Neale Lab, which removed participants whose self-reported sex differed from biological sex in the quality check (*Whole genome analysis pipeline*), so our findings only relate to cis men and women. Thirteenth, while overlapping samples for BMI and the outcomes pose a potential issue in the main analysis, we also replicated the analysis using sex-specific instruments for BMI independent of the UK Biobank, and results were similar, suggesting bias from overlapping samples is minimal. Consistently, overlapping samples have been shown to make most difference for relatively small samples and for MR-Egger estimates, particularly when the I^2_{GX} is low, leading to confounded estimates. (Minelli et al., 2021). Lastly, we used linear MR, so we cannot exclude the possibility of a "J" shaped association, however trials of incretins suggest a "J" curve may be a manifestation of bias (Wilding et al., 2021).

Public health implications

Trials of incretins have clearly indicated many benefits of weight loss particularly for older people (Leiter et al., 2019; Lincoff et al., 2023). Our study showing how BMI might increase risk of chronic diseases, reduce quality of life, and depress mental health in women, underscores the importance of addressing the obesity epidemic equitably in men and women, given differences by sex in some consequences of adiposity, such as psychological disorders, lipids and cancer. Overweight and obesity is more common in men than women in developed countries (Kanter & Caballero, 2012; Maruyama & Nakamura, 2018). With ongoing global economic development, the same pattern is likely to become more common. Currently women are more likely to seek medical intervention for weight management, such as semaglutide, than men (Luthra, 2023). To promote population health, it is important to address the unique challenges faced by overweight men and women. Men are at higher risk of heart disease and premature death due to high BMI, so targeted public health interventions, such as sex-specific weight recommendations or guidelines, could perhaps be considered.

Conclusion

Our contemporary systematic examination found BMI associated with a broad range of health-related attributes. We also found significant sex differences in many traits, underscoring the importance of addressing higher BMI in both men and women possibly as means of redressing differences in life expectancy. Ultimately, our study emphasizes the harmful effects of obesity and the importance of maintaining a healthy BMI. Whether BMI recommendations should differ by sex might be considered.

Data availability

This study used data from the MR-base platform (*https://www.mrbase.org/*), UK Biobank (*http://www.nealelab.is/uk-biobank/*).

Abbreviations

- ApoB: apolipoprotein B
- BMI: body mass index
- GIANT: Genetic Investigation of ANthropometric Traits
- GWAS: genome-wide association study

- HDL-c: high density lipoprotein cholesterol
- LDL: low density lipoprotein
- MR: Mendelian Randomization
- SHBG: sex hormone binding globulin

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Consent for publication

All participants were consent for publication.

Ethical approval

The study protocol was not pre-registered. We used only publicly available summary-level data and did not collect any original data in this study. Ethics approval and consent from individual participants can be found in the original publications.

Credit author statement

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Reviewer #1 (Public review):

Summary:

This study uses information from the UK Biobank and aims to investigate the role of BMI on various health outcomes, with a focus on differences by sex. They confirm the relevance of many of the well-known associations between BMI and health outcomes for males and females and suggest that associations for some endpoints may differ by sex. Overall their

conclusions appear supported by the data. The significance of the observed sex variations will require confirmation and further assessment.

Strengths:

This is one of the first systematic evaluations of sex differences between BMI and health outcomes.

The hypothesis that BMI may be associated with health differentially based on sex is relevant and even expected. As muscle is heavier than adipose tissue, and as men typically have more muscle than women, as a body composition measure BMI is sometimes prone to classifying even normal weight/muscular men as obese, while this measure is more lenient when used in women.

Confirmation of the many well-known associations is as expected and attests to the validity of their approach.

Demonstration of the possible sex differences is interesting, with this work raising the need for further study.

Weaknesses:

Many of the statistical decisions appeared to target power at the expense of quality/accuracy. For example, they chose to use self-reported information rather than doctor diagnoses for disease outcomes for which both types of data were available.

Despite known problems and bias arising from the use of one sample approach, they chose to use instruments from the UK Biobank instead of those available from the independent GIANT GWAS, despite the difference in sample size being only marginally greater for UKB for the context. With the way the data is presented, it is difficult to assess the extent to which results are compatible across approaches.

The approach to multiple testing correction appears very lenient, although the lack of accuracy in the reporting makes it difficult to know what was done exactly. The way it reads, FDR correction was done separately for men, and then for women (assuming that the duplication in tests following stratification does not affect the number of tests). In the second stage, they compared differences by sex using Z-test, apparently without accounting for multiple testing.

Presentation lacks accuracy in a few places, hence assessment of the accuracy of the statements made by the authors is difficult.

Conclusion "These findings highlight the importance of retaining a healthy BMI" is rather uninformative, especially as they claim that for some attributes the effects of BMI may be opposite depending on sex/gender.

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Reviewer #2 (Public review):

Summary:

In this present Mendelian randomization-phenome-wide association study, the authors found BMI to be positively associated with many health-related conditions, such as heart disease, heart failure, and hypertensive heart disease. They also found sex differences in some traits such as cancer, psychological disorders, and ApoB.

Strengths:

The use of the UK-biobank study with detailed phenotype and genotype information.

Weaknesses:

Previous studies have performed this analysis using the same cohort, with in-depth analysis. See this paper: Searching for the causal effects of body mass index in over 300,000 participants in UK Biobank, using Mendelian randomization. https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.1007951

I believe that the authors' claim, "To our knowledge, no sex-specific PheWAS has investigated the effects of BMI on health outcomes," is not well supported. They have not cited a relevant paper that conducted both overall and sex-stratified PheWAS using UK Biobank data with a detailed analysis. Given the prior study linked above, I am uncertain about the additional contributions of the present research.

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