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 **valuable** findings on Mendelian randomization-phenome-wide association, with BMI associated with health outcomes, and there is a focus on sex differences. The phenotype and genotype data are **convincing**. The work will be of interest to researchers and clinicians in epidemiology, public health and medicine.

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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 easily 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) using 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 203 of 680 traits in men, after adjusting for false discovery; differences by sex were found for 105 traits, and 46 traits

remained after adjusting for false discovery. BMI was more strongly positively associated with myocardial infarction, major coronary heart disease events, ischemic heart disease and heart attack in men than women. BMI was more strongly positively associated with apolipoprotein B (ApoB) and diastolic blood pressure in women than men.

Conclusion

Our study revealed that BMI might affect a wide range of health-related attributes and also highlights notable sex differences in its impact, including opposite associations for certain attributes, such as ApoB; and stronger effects in men, such as for cardiovascular diseases. Our findings underscore the need for nuanced, sex-specific policy related to BMI to address inequities in health.

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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 stronger effects in men, such as for cardiovascular diseases. Our findings underscore the need for nuanced, sex-specific policy related to 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 (Fewell et al., 2007). Mendelian randomization (MR) studies reduce confounding by using genetic proxies, such as single nucleotide polymorphisms (SNPs), for exposures (Smith & Ebrahim, 2003). Previous phenome-wide association studies using MR (MR-PheWASs) have identified impacts of sex-combined BMI on endocrine disorders, circulatory diseases, inflammatory and dermatological conditions, some biomarkers and feelings of nervousness (Hyppönen et al., 2019; Millard et al., 2019; Millard et al., 2015), but did not systematically use sex-specific BMI for the exposure or sex-specific outcomes. Previous MR studies and 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 (Hyppönen et al.,

2019; Millard et al., 2019; Millard et al., 2015). To address this gap, we conducted a sex-specific PheWAS, using the largest available sex-specific GWAS of BMI, to explore the impact of sex-specific BMI on sex-specific health-related attributes.

Methods

Data sources

Exposure: Body mass index

To obtain genetic information for BMI sex-specifically, we used BMI (inverse rank normalized) from two sources: a prospective cohort study of half a million adults from the UK Biobank, 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, while duplicate phenotypes were excluded. Where GWAS of very similar attributes were provided, we only included one instance. 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 electrocardiogram, which was only conducted in healthy people (Ramírez et al., 2021). Where attributes were available from both self-report and doctor diagnosis, we used self-reports. This is because comprehensive record linkage to doctor diagnoses has not yet been fully implemented for the UK Biobank, so information from doctor diagnoses may not fully represent the broader UK Biobank cohort. 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**.

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 based on the UK Biobank categories (*https://biobank.ndph.ox.ac.uk/ukb/cats.cgi*). Binary attributes with an International Classification

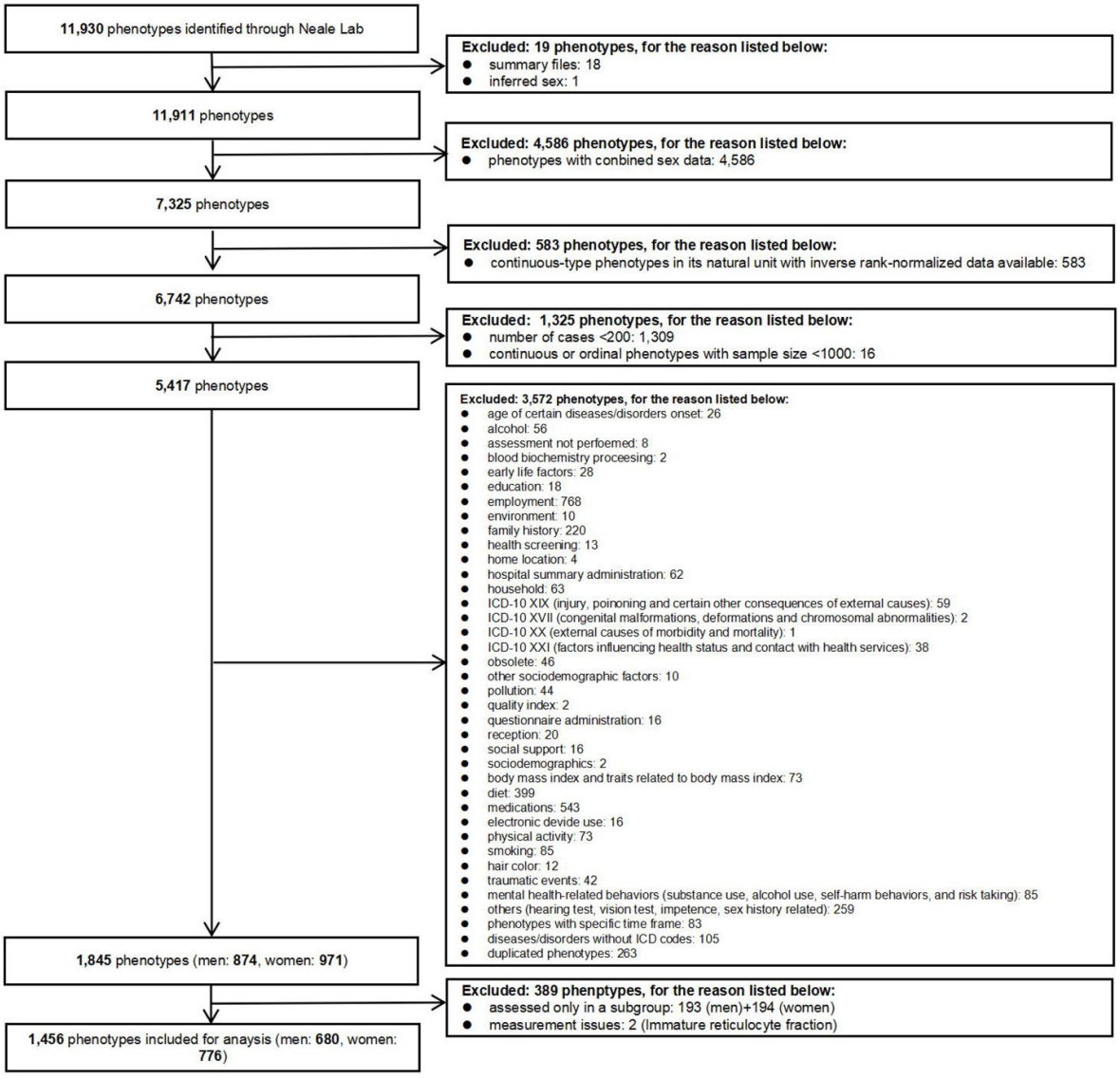

Figure 1.

Selection criteria for the phenotypes

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 effects of genetically predicted sex-specific BMI on each attribute considered sex-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 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 obtained differences by sex using a z-test (Paternoster et al., 1998), which as recommended was on a linear scale for dichotomous outcomes (Knol et al., 2007; Rothman, 2008), then we identified which ones remained after allowing for false discovery. We used the R packages "TwoSampleMR" (version: 0.6.1), "Mendelian Randomization" (version: 0.10.0) for the MR analysis and "metafor" (version: 4.6-0) to assess sex-differences.

Results

Initial analysis using sex-specific BMI from GIANT yielded similar estimates as when using sex-specific BMI from the UK Biobank but had fewer SNPs resulting in wider confidence intervals (S Table 1) and fewer significant associations (S Table 2). Analysis using sex-combined GIANT yielded more significant associations but lacks granularity, so we presented the results obtained using sex-specific BMI from the UK Biobank.

Sex-specific estimates

In men, BMI was associated with 203 of the 680 health-related attributes considered using false discovery (**Figure 2**, **S Table 2**). As expected, BMI was positively associated with ischemic heart disease, heart failure, hypertensive heart and/or renal disease, major coronary heart disease events, heart attack, diabetes, hypertension, sleep apnoea, daytime dozing/sleeping (narcolepsy), triglycerides, urinary potassium, urinary sodium and major surgeries. BMI was also inversely associated with age at recruitment, osteoporosis, hay fever and allergic rhinitis or eczema, high density lipoprotein cholesterol (HDL-c), cholesterol, low density lipoprotein cholesterol (LDL-c), 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 health-related attributes considered using the false discovery (**Figure 3**, **S Table 2**). As expected, BMI was positively associated with ischemic heart disease, heart failure, hypertensive heart and/or renal disease, heart attack, diabetes, hypertension, sleep apnoea, daytime dozing/sleeping (narcolepsy), 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-c and SHBG. BMI was

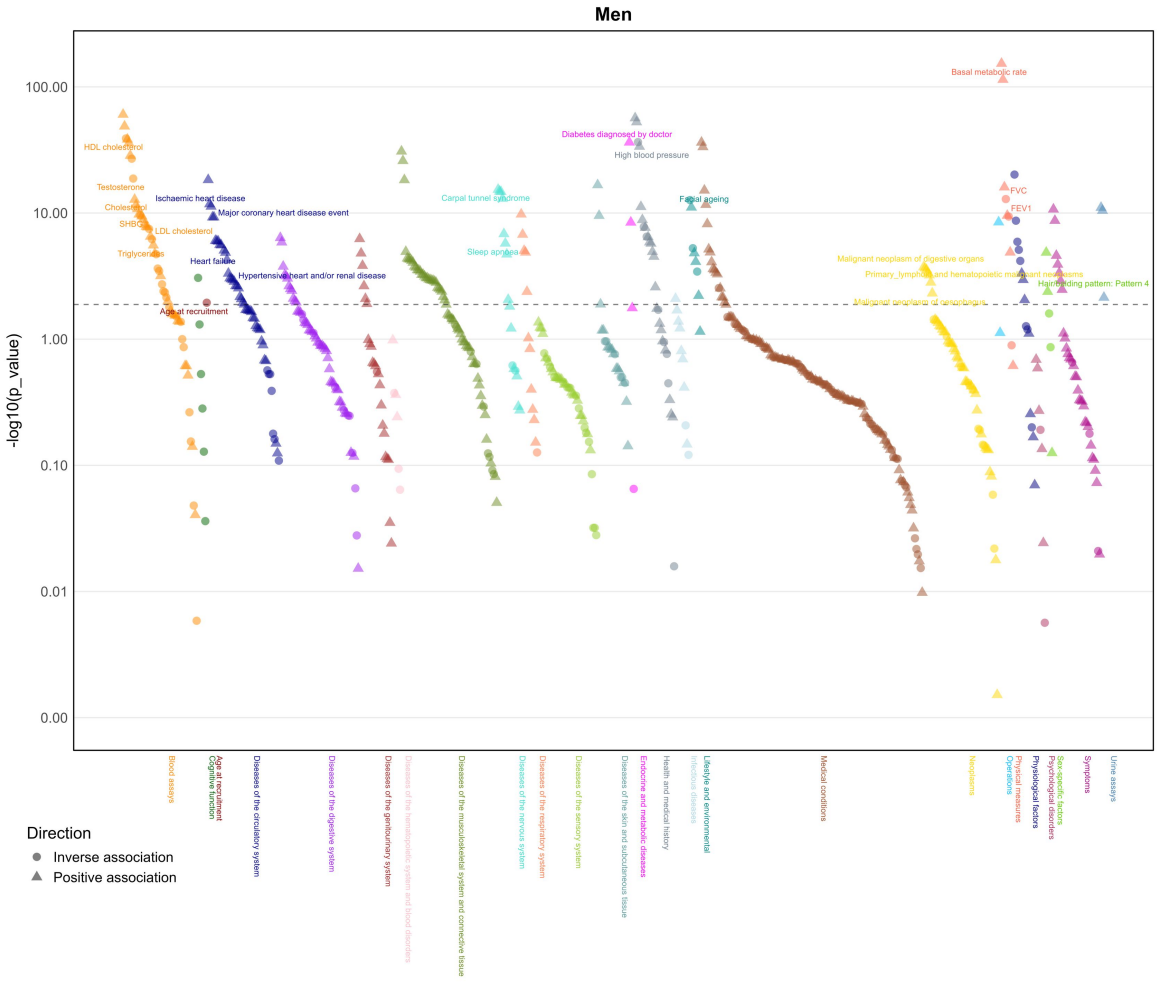

Figure 2.

Manhattan plot of body mass index on phenotypes in men (n: 167,020) from the UK Biobank. Note: The dotted lines indicate the significant threshold.

positively associated with risk of uterine/endometria 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 (p-value<0.05); 46 phenotypes remained after allowing for false discovery (**Table 1**). Of these 46 differences most (35) were in magnitude but not direction, such as for SHBG, ischemic heart disease, heart attack, and facial aging, while 11 were directionally different.

Notably, BMI was more strongly positively associated with myocardial infarction, major coronary heart disease events, ischemic heart disease, heart attack, and facial aging in men than in women. BMI was more strongly positively associated with diastolic blood pressure, and hypothyroidism/myxoedema in women than men. BMI was more strongly inversely associated with LDL-c, hay fever and allergic rhinitis or eczema in men than women. BMI was more strongly inversely associated with SHBG in women than men.

BMI was inversely associated with ApoB, iron deficiency anemia, hernia, and total testosterone in men, while positively associated with these traits in women (**Table 1**). BMI was inversely associated with sensitivity/hurt feelings, and ever seeking medical advice for nerves, anxiety, tension, or depression in men. However, BMI was positively associated with sensitivity/hurt feelings and ever seeking medical advice for these same issues in women. BMI was positively associated with muscle or soft tissue injuries and haemorrhage from respiratory passages in men, whilst inversely associated with these traits in women.

Of the 42 significant sex-specific associations identified in both the UK Biobank and the sex-specific GIANT consortium for men, all were directionally consistent. Similarly, for women, all 45 such significant associations were directionally consistent.

Discussion

Consistent with previous studies BMI was positively associated with many health-related attributes, such as ischemic heart disease, heart failure, hypertensive heart and/or renal disease, diabetes, hypertension and sleep apnoea. Our study adds by showing sex-differences in some traits related to 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 ischemic 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. 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 in women (although directionally consistent and not significant after allowing for false discovery). Another MR study found BMI positively associated with asthma and poorer lung function, but not with hay fever (Skaaby et al., 2018), while we found BMI inversely associated with hay fever and allergy allergic rhinitis or eczema in men, but not in women. Previous studies have shown BMI inversely associated with sodium/potassium (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 a previous MR study (Ardissino et al., 2022), we found BMI positively associated with sleep apnoea. We also found positive

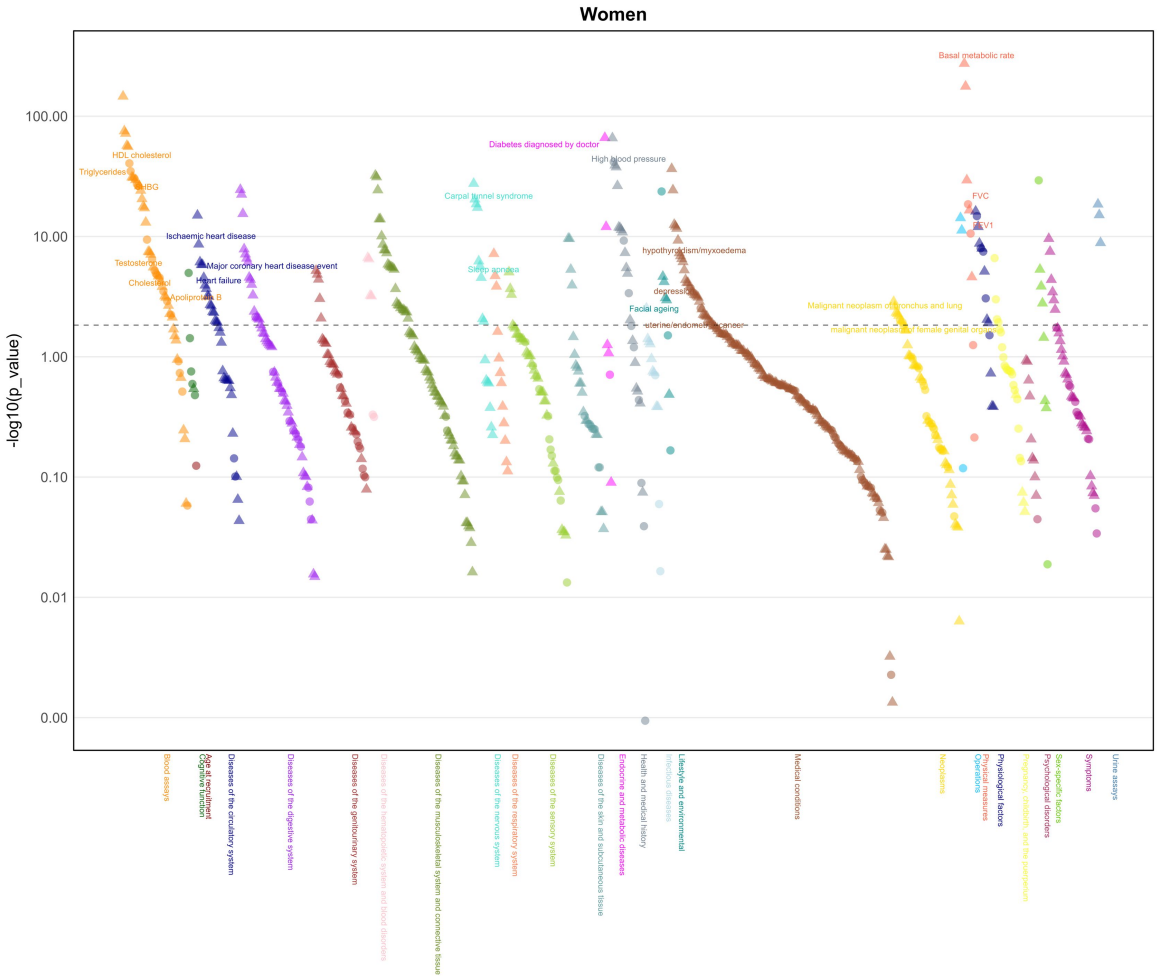

Figure 3.

Manhattan plot of body mass index on phenotypes in women (n: 194,174) from the UK Biobank. Note: The dotted lines indicate the significant threshold.

Category	Phenotypes	Men	Women	Sex-difference after false-discovery rate
Blood assays	SHBG	↓	↓	√
	Albumin	↓	↓	×
	Vitamin D	↓	↓	√
	Cholesterol	↓	↓	×
	Total bilirubin	↓	↓	×
	LDL cholesterol	↓	↓	√
	Direct bilirubin	↓	↓	√
	Platelet count	↓	↑	×
	Testosterone	↓	↑	√
	Apoliprotein B	↓	↑	√
	Platelet crit	↓	↑	√
	Aspartate aminotransferase	↑	↑	×
	Alkaline phosphatase	↑	↑	×
	Neutrophill count	↑	↑	×
	Red blood cell (erythrocyte) distribution width	↑	↑	×
	Triglycerides	↑	↑	×
	Urate	↑	↑	√
	C-reactive protein	↑	↑	√
Diseases of the circulatory system	Diagnoses - main ICD10: I35 Nonrheumatic aortic valve disorders	↑	↑	×
	Peripheral artery disease	↑	↑	√
	Death due to cardiac causes	↑	↑	×
	Heart failure,strict	↑	↑	×
	Diagnoses - main ICD10: I26 Pulmonary embolism	↑	↑	×
	DVT of lower extremities and pulmonary embolism	↑	↑	×
	Venous thromboembolism	↑	↑	×
	Myocardial infarction, strict	↑	↑	√
	Major coronary heart disease event	↑	↑	√
	Major coronary heart disease event excluding revascularizations	↑	↑	√
	Coronary atherosclerosis	↑	↑	√
	Ischaemic heart disease, wide definition	↑	↑	√
	Diseases of the circulatory system	↑	↑	×
Diseases of the	Diagnoses - main ICD10: K60	↑	↑	×

Table 1.

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

digestive system	Fissure and fistula of anal and rectal regions			
	Diagnoses - main ICD10: K81 Cholecystitis	↑	↑	×
	Hernia	↓	↑	√
	Diagnoses - main ICD10: K80 Cholelithiasis	↑	↑	√
	Disorders of gallbladder, biliary tract and pancreas	↑	↑	√
	Diseases of the digestive system	↑	↑	√
Diseases of the genitourinary system	Diagnoses - main ICD10: N17 Acute renal failure	↑	↑	×
	Diagnoses - main ICD10: N39 Other disorders of urinary system	↑	↑	√
Diseases of the hematopoietic system and blood disorders	Other anaemias	↓	↑	×
	Other and unspecified anaemias	↓	↑	×
	Iron deficiency anaemia	↓	↑	√
	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	↑	↑	√
Diseases of the musculoskeletal system and connective tissue	Cervicalgia	↓	↑	×
	Soft tissue disorders related to use, overuse and pressure	↑	↑	×
	Impingement syndrome of shoulder	↑	↑	×
	Pain in limb	↑	↑	√
	Other soft tissue disorders, not elsewhere classified	↑	↑	√
	Diagnoses - main ICD10: M79 Other soft tissue disorders, not elsewhere classified	↑	↑	√
Diseases of the nervous system	Diagnoses - main ICD10: G57 Mononeuropathies of lower limb	↓	↑	×
	Sleep apnoea	↑	↑	×
	Diagnoses - main ICD10: G47 Sleep disorders	↑	↑	×
	Carpal tunnel syndrome	↑	↑	×
	Nerve, nerve root and plexus disorders	↑	↑	×
Diseases of the respiratory system	Diagnoses - main ICD10: J18 Pneumonia, organism unspecified	↑	↑	√
	Diseases of the respiratory system	↑	↑	×
Diseases of the	Diagnoses - main ICD10: H61	↑	↓	×

Table 1. (continued)

sensory system	Other disorders of external ear			
	Degeneration of macula and posterior pole	↓	↑	×
Diseases of the skin and subcutaneous tissue	Diagnoses - main ICD10: L03 Cellulitis	↑	↑	√
Endocrine and metabolic diseases	Diabetes diagnosed by doctor	↑	↑	√
Health and medical history	Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor: Hayfever, allergic rhinitis or eczema	↓	↓	√
	Blood clot, DVT, bronchitis, emphysema, asthma, rhinitis, eczema, allergy diagnosed by doctor: None of the above	↑	↓	√
	Vascular/heart problems diagnosed by doctor: Heart attack	↑	↑	√
	Chest pain or discomfort	↑	↑	×
	Mouth/teeth dental problems: Dentures	↑	↑	×
Lifestyle and environmental	Morning/evening person (chronotype)	↓	↓	×
	Facial ageing	↑	↑	√
Medical conditions	Non-cancer illness code, self-reported: osteoporosis	↓	↓	×
	Non-cancer illness code, self-reported: headaches (not migraine)	↓	↑	×
	Non-cancer illness code, self-reported: pernicious anaemia	↓	↑	×
	Non-cancer illness code, self-reported: psoriatic arthropathy	↓	↑	×
	Non-cancer illness code, self-reported: eye/eyelid problem	↓	↑	×
	Non-cancer illness code, self-reported: allergy/hypersensitivity/anaphylaxis	↓	↑	×
	Non-cancer illness code, self-reported: ulcerative colitis	↑	↓	×

Table 1. (continued)

	Non-cancer illness code, self-reported: bladder problem (not cancer)	↓	↑	×
	Non-cancer illness code, self-reported: helicobacter pylori	↑	↑	×
	Non-cancer illness code, self-reported: muscle or soft tissue injuries	↑	↓	√
	Non-cancer illness code, self-reported: muscle/soft tissue problem	↓	↑	×
	Non-cancer illness code, self-reported: gout	↑	↑	√
	Non-cancer illness code, self-reported: cervical spondylosis	↑	↑	×
	Non-cancer illness code, self-reported: arthritis (nos)	↑	↑	×
	Non-cancer illness code, self-reported: unclassifiable	↓	↑	×
	Non-cancer illness code, self-reported: cholelithiasis/gall stones	↑	↑	√
	Non-cancer illness code, self-reported: depression	↑	↑	×
	Non-cancer illness code, self-reported: hypothyroidism/myxoedema	↑	↑	√
	Non-cancer illness code, self-reported: gastro-oesophageal reflux (gord) / gastric reflux	↑	↑	×
	Non-cancer illness code, self-reported: angina	↑	↑	√
	Non-cancer illness code, self-reported: asthma	↑	↑	√
	Non-cancer illness code, self-reported: osteoarthritis	↑	↑	×
Neoplasms	Malignant neoplasm of urinary organs	↑	↓	×
	Diagnoses - main ICD10: D35 Benign neoplasm of other and unspecified endocrine glands	↑	↑	×
	Malignant neoplasm of colon	↑	↓	×
	Lymphomas	↑	↑	×
	Malignant neoplasm of digestive	↑	↑	×

Table 1. (continued)

	organs			
Physical measures	Hand grip strength (right)	↑	↓	×
	Diastolic blood pressure, automated reading	↑	↑	√
Physiological factors	Sensitivity / hurt feelings	↓	↑	√
	Neuroticism score	↓	↑	×
	Seen doctor (GP) for nerves, anxiety, tension or depression	↓	↑	√
	Miserableness	↑	↑	√
	Loneliness, isolation	↑	↑	√
	Fed-up feelings	↑	↑	√
Symptoms	Diagnoses - main ICD10: R04 Haemorrhage from respiratory passages	↑	↓	√
	Diagnoses - main ICD10: R31 Unspecified haematuria	↑	↓	√
Urine assays	Potassium in urine	↑	↑	×

Stronger associations in women and different directions in men and women
Stronger associations in men and different directions in men and women
Stronger associations in women and same directions in men and women
Stronger associations in men and same directions in men and women

Table 1. (continued)

associations of BMI with daytime dozing in both sexes, which may indicate effects of BMI on quality of life. Higher BMI was also associated with a younger age at recruitment among men, suggesting poorer survival to recruitment in men than women given the GWAS adjusted for age and the short recruitment window makes period effects unlikely. The association of BMI with age at recruitment was less evident in women, with no significant sex difference. Consistently, a prior observational study found high BMI 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 common cardiovascular diseases 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 ApoB, a key heart disease risk factor, requires some explanation. BMI is a complex phenotype that may represent different attributes or have different consequences in men compared with women. Fat mass storage tends to differ between men and women (visceral versus subcutaneous) (Power & Schulkin, 2008). The causes of higher 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. Whether the difference in ischemic heart disease rates between men and women that emerged in the US and the UK the late 19th century (Nikiforov & Mamaev, 1998) is explained by rising BMI remains to be determined. 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 women, although the sex difference was not significant 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. We also considered false discovery for sex differences. 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 1,456), the MR-Egger intercept was significant while the IVW estimate was not (S Table 3), potentially indicating horizontal pleiotropic effects or the play of chance, which requires further investigation. Second, MR assesses 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 electrocardiogram (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 it 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. This may bias estimates towards the null or inverse for harmful binary outcomes (Thompson et al., 2013), but is less likely to affect 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 (Khan et al., 2023; Ruder, 2023). 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 1). Using sex-specific BMI from the UK Biobank and GIANT 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 from sex-combined GIANT (S Table 1) 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, whose quality check removed participants whose self-reported sex differed from their biological sex, 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. 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 overweight/obesity, such as psychological disorders and lipids. Being overweight or obese 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, such as for cardiovascular diseases, 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 nuanced, sex-specific policy related to BMI to address *inequities.in* health.

Data availability

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

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Additional information

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Consent for publication

All participants consented to publication in accordance with the original datasets (publicly available databases).

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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Abbreviations

- ApoB: apolipoprotein B
- BMI: body mass index
- ECG: electrocardiogram (ECG)
- GIANT: Genetic Investigation of ANthropometric Traits
- GWAS: genome-wide association study
- HDL-c: high density lipoprotein cholesterol
- LDL-c: low density lipoprotein cholesterol
- MR: Mendelian Randomization

- SHBG: sex hormone binding globulin

Additional files

Supplementary material

Note

This reviewed preprint has been updated to correct the display of Figures 2 and 3.

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Editors

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.

Comments on revisions:

I believe the authors have presented convincing arguments for the novelty and interpretation of their study. I have no additional comments.

https://doi.org/10.7554/eLife.102573.2.sa1

Author response:

The following is the authors' response to the original reviews

> ***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.*

Thank you for your positive comments. We have revised the analysis based on your feedback and that from the two reviewers. Specifically, we implemented a stricter multiple testing correction approach, improved the figures, included additional figures in the Supplementary

Materials, considered the sex differences more rigorously and reported them in more detail. A comprehensive description of the revisions is provided below.

> ***Public Reviews:***
>
> ***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.*

Thank you for your valuable comments. We are grateful for the time and effort you have devoted to reviewing our manuscript. We have strengthened our paper by adding your insightful comment about the rationale for sex-specific analysis to the introduction:

> *Weaknesses:*
>
> *(1) 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.*

Thank you for your valuable comments. We apologize for the lack of clarity in our original description of the phenotypes. Information about health in the UK Biobank was obtained at baseline from tests, measurements and self reports. Subsequently comprehensive data linkage to hospital admissions, death registries and cancer registries was implemented. However, data linkage to primary care data, such as doctor diagnoses, has not been comprehensively implemented for the UK Biobank, possibly for logistic reasons. Doctor diagnoses are only available for about half the cohort, (https://www.ukbiobank.ac.uk/enable-your-research/about-our-data/health-related-outcomes-data). So, we used self-reported diagnoses because they are substantially more comprehensive than the doctor diagnoses. We have explained this point by making the following change to the Methods:

“Where attributes were available from both self-report and doctor diagnosis, we used self-reports. This is because comprehensive record linkage to doctor diagnoses has not yet been fully implemented for the UK Biobank, so information from doctor diagnoses may not fully represent the broader UK Biobank cohort.”

> *(2) 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.*

Thank you for your comments. We agree completely about the issues with a one sample approach, please accept our apologies for not explaining our rationale. The sex-specific GIANT GWAS study is similar in size to the UK Biobank GWAS. However, the sex-specific GIANT GWAS is much less densely genotyped (~2,5 million variants) than the sex-specific UK Biobank GWAS (~10 million variants), so has less power, hence our use of the UK Biobank. To make this clear, we have added the number of variants in each study to the method section. Nevertheless, we also repeated analysis using sex-specific GIANT, as now given in the methods by making the following change

We amended the description in the first paragraph of the results section:

"Initial analysis using sex-specific BMI from GIANT yielded similar estimates as when using sex-specific BMI from the UK Biobank but had fewer SNPs resulting in wider confidence intervals (S Table 1) and fewer significant associations (S Table 1). Analysis using sex-combined GIANT yielded more significant associations but lacks granularity, so we presented the results obtained using sex-specific BMI from the UK Biobank."

In the discussion we also made the following changes:

"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 1). Using sex-specific BMI from the UK Biobank and GIANT 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 from sex-combined GIANT (S Table 1) makes the results more comparable to previous similar studies."

> *(3) 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.*

Thank you, we have accounted for multiple comparisons when considering differences by sex and have made corresponding changes. Specifically, in the methods, we changed:

"We obtained differences by sex using a z-test (Paternoster et al., 1998), which as recommended was on a linear scale for dichotomous outcomes (Knol et al., 2007; Rothman, 2008), then we identified which ones remained after allowing for false discovery"

We have made the following changes to the results section:

"We found significant differences by sex in the associations of BMI with 105 health-related attributes (p-value<0.05); 46 phenotypes remained after allowing for false discovery (Table 1). Of these 46 differences most (35) were in magnitude but not direction, such as for SHBG, ischemic heart disease, heart attack, and facial aging, while 11 were directionally different.

Notably, BMI was more strongly positively associated with myocardial infarction, major coronary heart disease events, ischemic heart disease, heart attack, and facial aging in men than in women. BMI was more strongly positively associated with diastolic blood pressure, and hypothyroidism/myxoedema in women than men. BMI was more strongly inversely

associated with LDL-c, hay fever and allergic rhinitis in men than women. BMI was more strongly inversely associated with SHBG in women than men.

BMI was inversely associated with ApoB, iron deficiency anemia, hernia, and total testosterone in men, while positively associated with these traits in women (Table 1). BMI was inversely associated with sensitivity/hurt feelings, and ever seeking medical advice for nerves, anxiety, tension, or depression in men. However, BMI was positively associated with sensitivity/hurt feelings and ever seeking medical advice for these same issues in women. BMI was positively associated with muscle or soft tissue injuries and haemorrhage from respiratory passages in men, whilst inversely associated with these traits in women."

We have correspondingly amended the discussion to reflect these changes by adding:

"Whether the difference in ischemic heart disease rates between men and women that emerged in the US and the UK the late 19th century (Nikiforov & Mamaev, 1998) is explained by rising BMI remains to be determined."

> *(4) Presentation lacks accuracy in a few places, hence assessment of the accuracy of the statements made by the authors is difficult.*

Thank you, we have revised the whole manuscript in order to improve clarity.

> *(5) Conclusion (Abstract) "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.*

Thank you for your comments. We have changed the conclusion of the abstract, as given below:

"Our study revealed that BMI might affect a wide range of health-related attributes and also highlights notable sex differences in its impact, including opposite associations for certain attributes, such as ApoB; and stronger effects in men, such as for cardiovascular diseases. Our findings underscore the need for nuanced, sex-specific policy related to BMI to address inequities in health.".

We have changed the Impact statement, as given below:

"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 stronger effects in men, such as for cardiovascular diseases. Our findings underscore the need for nuanced, sex-specific policy related to BMI."

We have changed the conclusion of the paper, as given below:

"Our contemporary systematic examination found BMI associated with a broad range of health-related attributes. We also found significant sex differences in many traits, such as for cardiovascular diseases, 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 nuanced, sex-specific policy related to BMI to address inequities.in health."

> ***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.*

Thank you for your valuable comments. We are grateful for the time and effort you have devoted to reviewing our manuscript.

> *Weaknesses:*
>
> *(1) 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.10079i51*

Thank you for your valuable comments. We checked the paper carefully. It gives sex-specific estimates when the outcome was assessed in different ways in men and women, for example the question about number of children was asked in terms of live births in women and number of children fathered in men. In addition, for some significant findings, the authors investigated differences by sex. However, the paper did not use sex-specific BMI or sex-specific outcomes systematically. We have added this paper to our introduction and amended the text to explain the novelty of our study compared to previous studies.

“Previous phenome-wide association studies using MR (MR-PheWASs) have identified impacts of sex-combined BMI on endocrine disorders, circulatory diseases, inflammatory and dermatological conditions, some biomarkers and feelings of nervousness (Hyppönen et al., 2019; Millard et al., 2015; Millard et al. 2019), but did not systematically use sex-specific BMI for the exposure or sex-specific outcomes.”

> *(2) 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.*

Thank you for your valuable comments, please accept our apologies for this oversight. As explained above, we have checked very carefully. There are three previous PheWAS for BMI, Hyppönen et al., 2019, Millard et al., 2015 and Millard et al. 2019. Hyppönen et al., 2019 and Millard et al., 2015 are not sex-specific. Millard et al. 2019 used sex-combined instruments, but some sex-specific outcomes, when the questions were asked sex-specifically, such as age at puberty asked as “age when periods started (menarche)” in women and “relative age of first facial hair” and “relative age voice broke” in men. When they found a factor significantly associated with BMI, they sometimes analyze it further including sex-specific analysis, but they did not do the analysis systematically for men and women with sex-specific BMI and sex-specific outcomes. We have amended the introduction to clarify this point.

“To our knowledge, no sex-specific PheWAS has investigated the effects of BMI on health outcomes (Hyppönen et al., 2019; Millard et al., 2015; Millard et al. 2009). To address this gap, we conducted a sex-specific PheWAS, using the largest available sex-specific GWAS of BMI, to explore the impact of sex-specific BMI on sex-specific health-related attributes”

> ***Recommendations for the authors:***

> ***Reviewer #1 (Recommendations for the authors):***
>
> *Presentation, accuracy, and referencing:*
>
> *(1) The quality of the English language needs to be checked, including that all sentences carry all components required (including verbs).*

We thank the reviewer for this suggestion. The manuscript has undergone language editing by a native English-speaker, with particular attention to grammatical completeness (including verb consistency and sentence structure). We have also clarified ambiguities and inconsistencies in terms pointed out by the native English speakers. All revisions have been implemented in the updated manuscript.

> *(2) The accuracy of statements needs to be checked. For example, in lines 82-83 it is not true that 2015/2019 was 'before the advent of large-scale GWAs studies". In the context of the above in lines 83-85, how can reference be made to a study published in 2020 calling that 'previous' MR studies and how a trial published in 2016 is 'recent'? Please revise, and please also check the manuscript for any other issues with accuracy of this kind.*

We thank the reviewer for this suggestion. We have checked the manuscript and revised these sentences to be clearer, by making the following change.

“Previous phenome-wide association studies using MR (MR-PheWASs) have identified impacts of sex-combined BMI on endocrine disorders, circulatory diseases, inflammatory and dermatological conditions, some biomarkers and feelings of nervousness (Hyppönen et al., 2019; Millard et al., 2015; Millard et al. 2019), but did not systematically use sex-specific BMI for the exposure or sex-specific outcomes. Previous MR studies and trials of incretins have expanded our knowledge about a broad range of effects of BMI (Larsson et al., 2020; Marso et al., 2016).”

> *(3) The adequacy of referencing will need to be checked, e.g. line 136 "as recommended by UK biobank" is vague and needs to be referenced.*

We thank the reviewer for this suggestion. We have added citations.

“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, based on the UK Biobank categories (https://biobank.ndph.ox.ac.uk/ukb/cats.cgi).”

> *(4) The accurate use of terminology needs to be checked. For example, BMI is a measure of adiposity, while high BMI (typically >30) is used to index obesity.*

We thank you for your comments. We have changed the descriptions into “overweight/obesity” throughout.

> *(5) Figure 1, Please check that complete information is given for 'selection criteria' and that the rationale for all information included is clear. For example, it is currently unclear what is the distinction between the bottom two sections which both present a number of features included in the analyses? Also, the Box detailing exclusion of 3585 variables does not give the criteria for these exclusions. Please add.*

Thank you for your comments. We have represented and revised Figure 1. Specifically, we have revised the bottom two sections to give each reason for exclusion and the number

excluded for that reason. The updated “Excluded: 3,572 phenotypes, for the reason listed below:” box now contains bullet-points giving each reason for exclusion in the box (e.g. age of certain diseases/disorders onset: 26, alcohol: 56).

> *(6) Figure 4, does not look to be of typical publication quality.*

We thank you for your comments. We have used different colors to make it smaller and more readable. Please see Table 1.

> *Analyses:*
>
> *(1) As it stands, it is very difficult for a reader to confirm the conclusion that similar findings are obtained both when using instruments from the UKB and GIANT based on data presented (Stable 1 and 2). I suggested two things.*
>
> *a) Organise stable 1 and 2 by significance and category, with separation by highlighting for those which are significant under correction. I would consider merging these two tables, such that it would be easy for the reader to make the comparisons side by side. Consider presenting separate tables for the analyses for women and men.*

We thank you for your comments. We have followed your helpful advice and merged S Table 1 and S Table 2 into S Table 1. Furthermore, we have also merged S Table 5 to S Table 1.

> *b) In Stable 3, please add information from related comparisons using the GIANT instruments. To support the authors' claim that associations are similar, but only the precision of estimation differed, you could consider adding information for numbers of associations for those that are directionally consistent and which have an association at least under nominal significance'. For associations where this does not hold, I would refrain from making a claim that the results are not affected by the choice of instrument (or biases relating to the analysis conducted).*

We thank you for your comments. Among 42 significant sex-specific associations identified in both the UK Biobank and the sex-specific GIANT consortium for men, all showed consistent directions of effect. Similarly, for women, all of the 45 significant associations exhibited consistent directions for UK Biobank compared with GIANT instruments.

In the sex-specific UK Biobank, there are 203 significant associations in men, and 232 significant associations in women. We have added: in the sex-specific GIANT, there are 46 significant associations in men, and 84 significant associations in women. In the sex-combined GIANT, there are 246 significant associations in men, and 276 significant associations in women. We have provided all this information in S Table 2.

We added the following descriptions at the end of the results section:

“Of the 42 significant sex-specific associations identified in both the UK Biobank and the sex-specific GIANT consortium for men, all were directionally consistent. Similarly, for women, all 45 such significant associations were directionally consistent.

We amended the following descriptions in the first paragraph of the results section:

“Initial analysis using sex-specific BMI from the GIANT yielded similar estimates as when using sex-specific BMI from the UK Biobank but had fewer SNPs resulting in wider confidence intervals (S Table 1) and fewer significant associations (S Table 2). Analysis using sex-combined GIANT yielded more significant associations but lacks granularity, so we presented the results obtained using sex-specific BMI from the UK Biobank.”

In the methods, we changed:

"We obtained differences by sex using a z-test (Paternoster et al., 1998), which as recommended was on a linear scale for dichotomous outcomes (Knol et al., 2007; Rothman, 2008), then we identified which ones remained after allowing for false discovery."

We have made the following changes to the results section:

"We found significant differences by sex in the associations of BMI with 105 health-related attributes (p-value<0.05); 46 phenotypes remained after allowing for false discovery (Table 1). Of these 46 differences most (35) were in magnitude but not direction, such as for SHBG, ischemic heart disease, heart attack, and facial aging, while 11 were directionally different.

Notably, BMI was more strongly positively associated with myocardial infarction, major coronary heart disease events, ischemic heart disease, heart attack, and facial aging in men than in women. BMI was more strongly positively associated with diastolic blood pressure, and hypothyroidism/myxoedema in women than men. BMI was more strongly inversely associated with LDL-c, hay fever and allergic rhinitis in men than women. BMI was more strongly inversely associated with SHBG in women than men.

BMI was inversely associated with ApoB, iron deficiency anemia, hernia, and total testosterone in men, while positively associated with these traits in women (Table 1). BMI was inversely associated with sensitivity/hurt feelings, and ever seeking medical advice for nerves, anxiety, tension, or depression in men. However, BMI was positively associated with sensitivity/hurt feelings and ever seeking medical advice for these same issues in women. BMI was positively associated with muscle or soft tissue injuries and haemorrhage from respiratory passages in men, whilst inversely associated with these traits in women."

> *(2) It is not clear what statistical criteria were used to determine sex differences, and the strategy/presentation should be clarified. In lines 229-231, it is implied that the 'significance' in one gender, but not in the other is used to indicate a difference. However, 'comparison of p-values' is not a valid statistical approach, and a more formal test (accounting for multiple testing would be warranted). It may be that a systematic approach has been implemented, but please check that it is adequately and accurately described to the reader.*

Please accept our apologies for being unclear. Multiple comparisons are for independent phenotypes however, here, some phenotypes cannot be independent, therefore, using multiple comparisons in men and women separately is quite strict. We added multiple comparisons for the assessment of sex-differences, which is now given in Table 1. Initially, there were 105 significant associations (p value for sex-difference<0.05) (Table 1), and 46 associations remained after FDR correction (Table 1).

Furthermore, we have made additional minor changes to clarify the wording.

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