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Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies

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Abstract

Background: Obesity is a worldwide epidemic that has been associated with a plurality of diseases in observational studies. The aim of this study was to summarize the evidence from Mendelian randomization (MR) studies of the association between body mass index (BMI) and chronic diseases.

Methods: PubMed and Embase were searched for MR studies on adult BMI in relation to major chronic diseases, including diabetes mellitus; diseases of the circulatory, respiratory, digestive, musculoskeletal, and nervous systems; and neoplasms. A meta-analysis was performed for each disease by using results from published MR studies and corresponding de novo analyses based on summary-level genetic data from the FinnGen consortium (n = 218,792 individuals).

Results: In a meta-analysis of results from published MR studies and de novo analyses of the FinnGen consortium, genetically predicted higher BMI was associated with increased risk of type 2 diabetes mellitus, 14 circulatory disease outcomes, asthma, chronic obstructive pulmonary disease, five digestive system diseases, three musculoskeletal system diseases, and multiple sclerosis as well as cancers of the digestive system (six cancer sites), uterus, kidney, and bladder. In contrast, genetically predicted higher adult BMI was associated with a decreased risk of Dupuytren's disease, osteoporosis, and breast, prostate, and non-melanoma cancer, and not associated with Alzheimer's disease, amyotrophic lateral sclerosis, or Parkinson's disease.

Conclusions: The totality of the evidence from MR studies supports a causal role of excess adiposity in a plurality of chronic diseases. Hence, continued efforts to reduce the prevalence of overweight and obesity are a major public health goal.

Keywords: Body mass index, Cancer, Cardiovascular disease, Chronic diseases, Obesity

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Background

Obesity is a worldwide epidemic that has been associated with an increased risk of a plurality of chronic diseases in traditional observational studies [1–6]. These observational findings [1–6] may represent the causal effect of obesity on disease risk or confounding from other risk factors, such as a poor diet and physical inactivity. During the last years, an increasing number of Mendelian randomization (MR) studies of adiposity, mostly defined by body mass index (BMI), in relation to chronic diseases have been published [7–53]. MR is an instrumental variable analysis that exploits genetic variants with a robust impact on the exposure (e.g., BMI) as proxy markers for the exposure to test whether the exposure has a causal relationship with disease risk [54]. Compared with conventional observational studies, MR studies are less susceptible to confounding as genes are randomly assorted when passed from parents to descendants [54]. Additionally, MR studies are not biased by reverse causality as genes are constant and not modified by disease development.

The aim of this study was to conduct a systematic review and meta-analyses of MR studies to determine the causal role of excess adiposity in chronic diseases. Meta-analyses were performed using results from published MR studies and complemented with results from de novo MR analyses of pertinent disease outcomes in the FinnGen consortium.

Methods

Literature search and inclusion criteria

A search in the PubMed and Embase databases using the query "(Mendelian randomization) AND (body mass index OR overweight OR obesity or adiposity)" was performed on October 3, 2021. Eligible for inclusion were original articles that reported estimates from an MR analysis of genetically predicted adulthood BMI in relation to one or more chronic diseases in the following disease groups: diabetes mellitus (type 1 or type 2); disease of the circulatory, respiratory, digestive, musculoskeletal, or nervous system; or site-specific cancer. When more than one study was published on the same outcome and study population, the study based on the largest number of cases or the largest number of genetic variants (if the sample size was the same) was included. No restriction based on the number of cases was imposed.

Data extraction and quality assessment

Data were extracted and entered in predefined tables by one author (SCL) and independently reviewed by another author (SB). From each MR study, the following information was extracted: the last name of the first author and year of publication; the number of single-nucleotide polymorphisms (SNPs) used as instrumental variables in the analysis, the source for the SNPs, and the exposure unit; consortium, study, or studies from which the SNP-outcome association estimates were obtained; the number of cases and non-cases or the total number of participants; ancestry of the study population; and the relative risk estimate (generally odds ratio [*OR*]) with 95% confidence interval (*CI*) for the BMI-outcome association from the primary analysis. The study quality was assessed by adapting a modified version of the Strengthening the Reporting of Mendelian Randomization Studies (STROBE-MR) Guidelines [55, 56].

Statistical analysis

In most studies, the relative risk estimate was expressed per 1 standard deviation (*SD*; ~4.8 kg/m^2) increase in genetically predicted BMI. For studies using another unit (e.g., 1 kg/m^2), the estimate was rescaled to 1 *SD* increase in BMI. Meta-analysis was performed for each outcome using results of published MR studies and de novo MR analyses of summary-level genetic data from the R5 release of the FinnGen consortium (n = 218,792 individuals) [57]. For the de novo MR analyses of FinnGen data, independent SNPs (low linkage disequilibrium R^2 < 0.001) associated with BMI at $P < 5 \times 10^{-8}$ in a genome-wide association meta-analysis of the Genetic Investigation of ANthropometric Traits consortium and the UK Biobank (n = 806,810 individuals) [58] were obtained from a recent MR study [49]. All BMI-associated SNPs were harmonized with the outcome data in FinnGen to ensure that effect estimates of each SNP on BMI and the outcome corresponded to the same effect allele. Analyses of FinnGen data were performed for all relevant diseases except aortic valve stenosis and osteoarthritis which were not available in the FinnGen database. Considering potential differential associations of BMI with disease risk in populations of different origins, sensitivity analyses confined to data based on European populations were conducted. Meta-analyses of results in non-European populations were not possible due to a lack of data from more than one study on the same disease. Heterogeneity between studies was quantified using the I^2 statistic [59]. Values <25%, 25–75%, and >75% were considered low, moderate, and high heterogeneity. All statistical analyses were conducted in Stata (StataCorp, College Station, TX, USA) using the mrrobust and metan commands.

Results

Literature search and study selection

The PubMed and Embase searches resulted in 1469 unique hits of which 116 articles reported results from an MR study of BMI in relation to one or more of the

pertinent disease outcomes. An overview of study selection is presented in Fig. 1.

Study quality and description

The results from the evaluation of study quality are provided in Additional file 1: Table S1. All studies indicated Mendelian randomization in the title and/or abstract, provided a rationale for the study and the objective, and provided information on the data sources used. In two studies, information on the number of cases and non-cases for the disease outcome(s) was not found [25, 29, 30]. Most studies obtained genetic instruments for BMI from a genome-wide association study based on the Genetic Investigation of ANthropometric Traits consortium with or without UK Biobank [58, 60, 61] and used 14 to several hundred SNPs as instrumental variables. The remaining studies used one to few selected SNPs in relevant obesity loci (e.g., *FTO*). Most recent MR studies used a strict linkage disequilibrium cut-off ($R^2 < 0.001$) to select independent SNPs as instrumental variables for BMI, but some studies selected all conditional independent SNPs identified in the genome-wide association study. The majority of MR studies were based on outcome data from one or few studies (e.g., Danish, Swedish, and Chinese cohorts), a large-scale genetic consortium, or the UK Biobank. For several outcomes, two or more studies were published based on outcome data from the same source population (e.g., same consortium or UK Biobank). One two-sample MR study did not indicate the statistical method used for the primary analysis [14], and eight studies did report results of sensitivity analyses based on robust MR methods (e.g., weighted median and MR-Egger regression) [9, 11, 17, 24, 25, 35, 40, 41].

The number of MR studies based on independent study samples for each disease category was two for

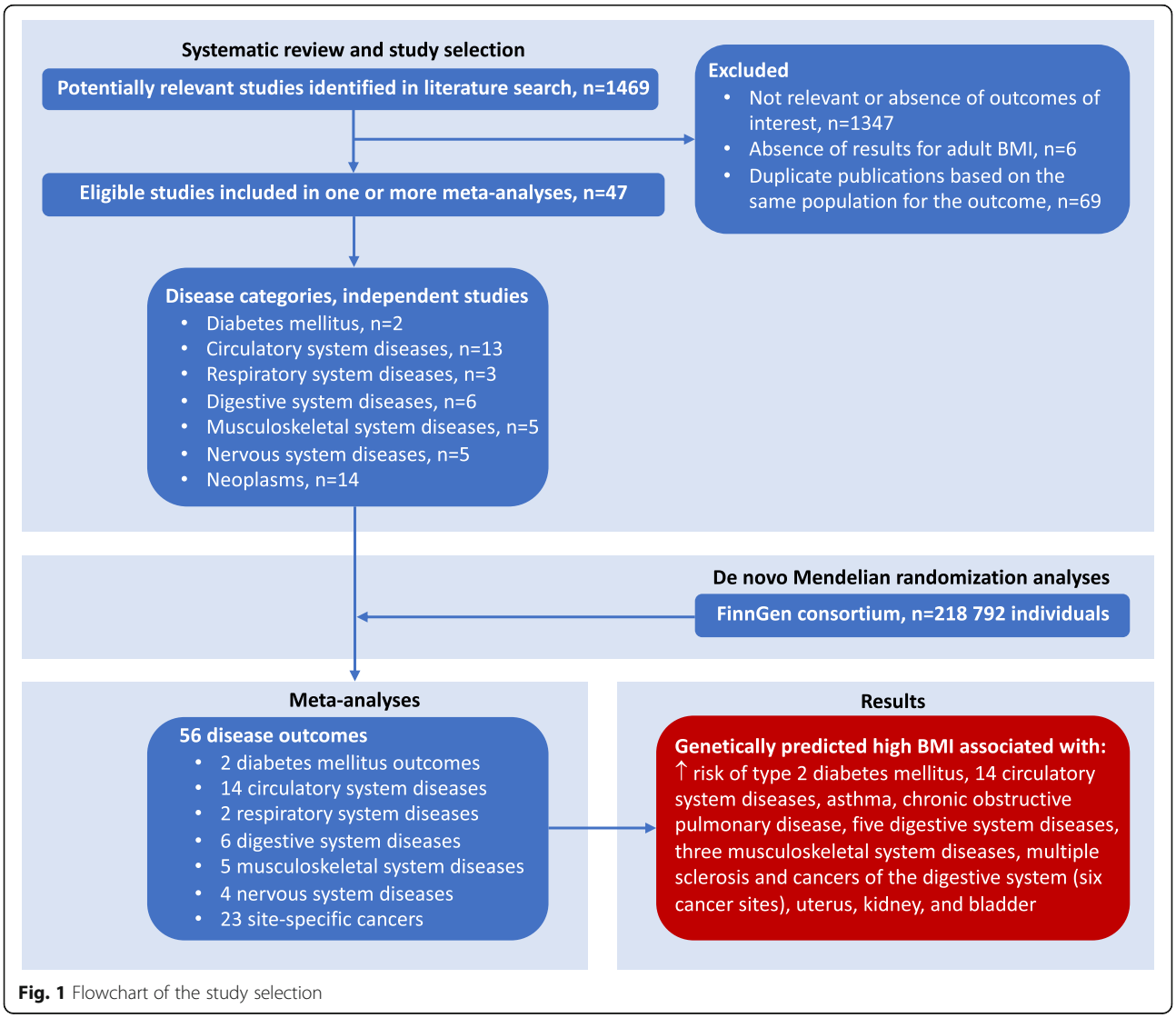

Fig. 1 Flowchart of the study selection

diabetes mellitus [7, 8], 13 for circulatory system diseases [9–21], three for respiratory diseases [8, 22, 23], six for digestive system diseases [24–29], five for musculoskeletal system diseases [30–34] plus FinnGen consortium (for osteoporosis), five for nervous system diseases [35–39], and 14 for neoplasms [40–53]. Among the selected studies, six studies included East-Asian (Chinese [11, 25, 42] and Japanese [48, 50]) or Chilean [53] individuals, whereas the remaining studies included individuals of European ancestry or mixed (trans-ancestry) populations. Details and results of published MR studies included in the meta-analyses as well as results from de novo MR analyses of FinnGen data are provided in Additional file 1: Table S2.

Diabetes mellitus

Genetically predicted higher BMI was associated with an increased risk of type 1 diabetes mellitus in UK Biobank but not in the FinnGen consortium, with high heterogeneity between studies (Additional file 1: Table S2). On the other hand, there was a consistent association of genetically predicted adulthood BMI with type 2 diabetes, with a combined *OR* of 2.03 (*95% CI* 1.88–2.19) (Additional file 1: Table S2).

Diseases of the circulatory system

Genetically predicted higher BMI was associated with increased risk of all 14 studied diseases of the circulatory system (Fig. 2, Additional file 1: Table S2). The strongest associations were for aortic valve stenosis (*OR* 2.02, *95% CI* 1.46–2.79), followed by heart failure (*OR* 1.69, *95% CI* 1.57–1.82) and hypertension (*OR* 1.68, *95% CI* 1.59–1.78). The associations were weaker for all stroke types, with *OR*s ranging from 1.16 (*95% CI* 1.10–1.23) for ischemic stroke to 1.21 (*95% CI* 1.02–1.44) for intracerebral hemorrhage. Excluding the study based on a Chinese population had a minor impact on the results for peripheral artery disease (*OR* 1.65, *95% CI* 1.55–1.75). High heterogeneity between studies was only observed in the analyses of aortic valve stenosis, atrial fibrillation, and hypertension, but this was due to different magnitude of positive associations rather than a lack of association in one of the studies (Additional file 1: Table S2).

Diseases of the respiratory system

MR studies on diseases of the respiratory system were scarce, with results reported only for asthma and chronic obstructive pulmonary disease (COPD) mortality (Additional file 1: Table S2). In a meta-analysis of available independent study samples, the *OR* was 1.36 (*95% CI* 1.29–1.43) for asthma and 1.65 (*95% CI* 1.47–1.85) for COPD, with no heterogeneity among studies.

Diseases of the digestive system

Genetically predicted higher BMI was associated with an increased risk of diverticular disease, gallstone disease, gastroesophageal reflux disease, Crohn's disease, and nonalcoholic fatty liver disease, but with a lower risk of ulcerative colitis (Fig. 3, Additional file 1: Table S2). The strongest association was for nonalcoholic fatty liver disease (*OR* 1.81, *95% CI* 1.22–2.69). Results for gallstone disease remained essentially unchanged after removing the study based on a Chinese population (Additional file 1: Table S2). Moderate heterogeneity between studies was only observed in the analysis of gastroesophageal reflux disease.

Diseases of the musculoskeletal system

Published MR studies of BMI and diseases of the musculoskeletal diseases were available for Dupuytren's disease, gout, osteoarthritis, and rheumatoid arthritis (Additional file 1: Table S2). Higher genetically predicted BMI was associated with a decreased risk of Dupuytren's disease but with an increased risk of the other three musculoskeletal diseases. The combined *OR*s were 0.77 (*95% CI* 0.69–0.87) for Dupuytren's disease, 1.92 (*95% CI* 1.60–2.30) for gout, 1.55 (*95% CI* 1.43–1.69) for osteoarthritis, and 1.27 (*95% CI* 1.17–1.39) for rheumatoid arthritis. There was high heterogeneity between studies on Dupuytren's disease and moderate heterogeneity between studies on gout and rheumatoid arthritis. MR analysis of osteoporosis in the FinnGen consortium showed an *OR* of 0.81 (*95% CI* 0.65–0.99) per 1 *SD* increase in genetically predicted BMI (Additional file 1: Table S2).

Diseases of the nervous system

Genetically predicted BMI was associated with multiple sclerosis (*OR* 1.26, *95% CI* 1.14–1.39) but not Alzheimer's disease or amyotrophic lateral sclerosis (Additional file 1: Table S2). There was heterogeneity between estimates for Parkinson's disease, with an inverse association of genetically predicted BMI and Parkinson's disease found in the FinnGen consortium (*OR* 0.76, *95% CI* 0.60–0.96) but not in the Parkinson's disease genome-wide association study (*OR* 0.96, *95% CI* 0.83–1.12). The combined *OR* of Parkinson's disease was 0.90 (*95% CI* 0.79–1.02).

Neoplasms

Meta-analysis results showed that genetically predicted BMI was associated with an increased risk of cancers of the digestive system (i.e., esophageal, stomach, colorectal, pancreatic, liver, and gallbladder/biliary tract cancer), uterus (endometrial and cervical cancer), ovary, kidney, and bladder, but with a decreased risk of breast, prostate, and non-melanoma skin cancer (Fig. 4). There was no consistent and overall association with other cancers

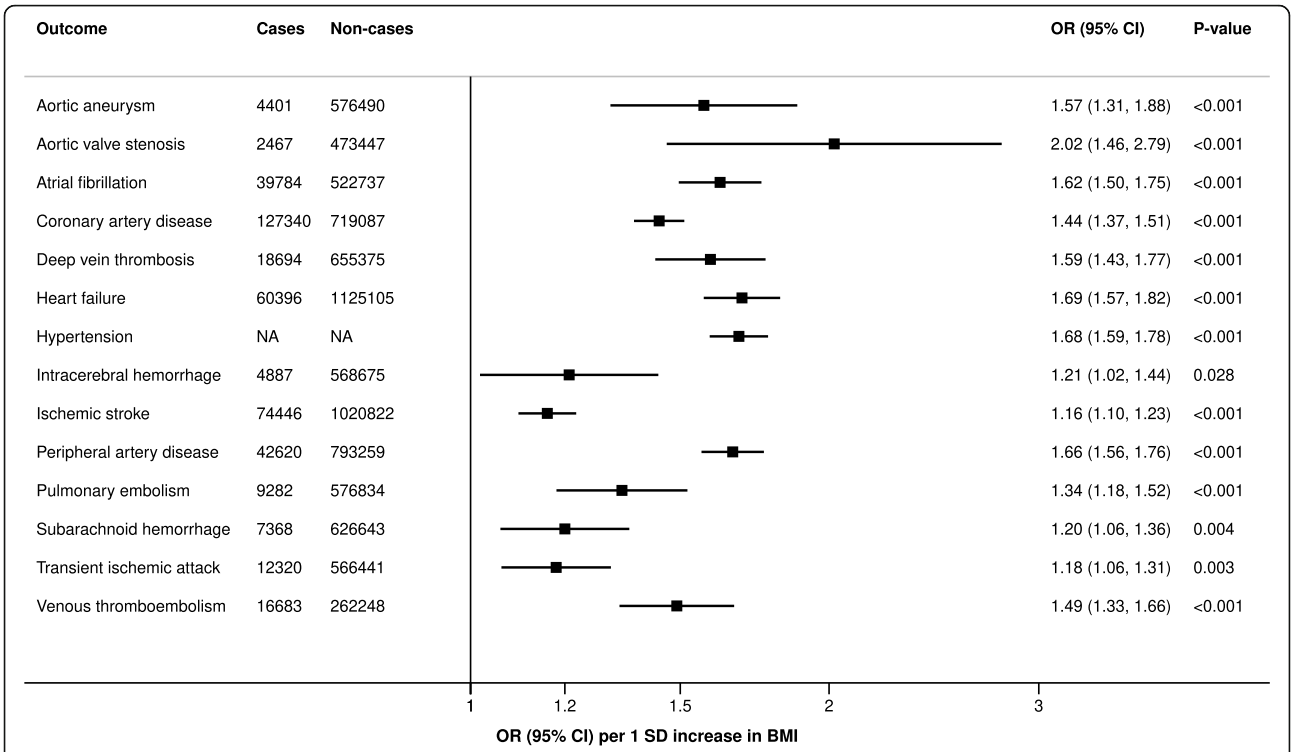

Fig. 2 Meta-analysis results for genetically predicted BMI in relation to diseases of the circulatory system. Results are scaled per 1 *SD* increase of BMI. Analyses of coronary artery disease and peripheral artery disease include individuals of both European (the vast majority) and non-European ancestry; analyses of other outcomes include individuals of European ancestry only

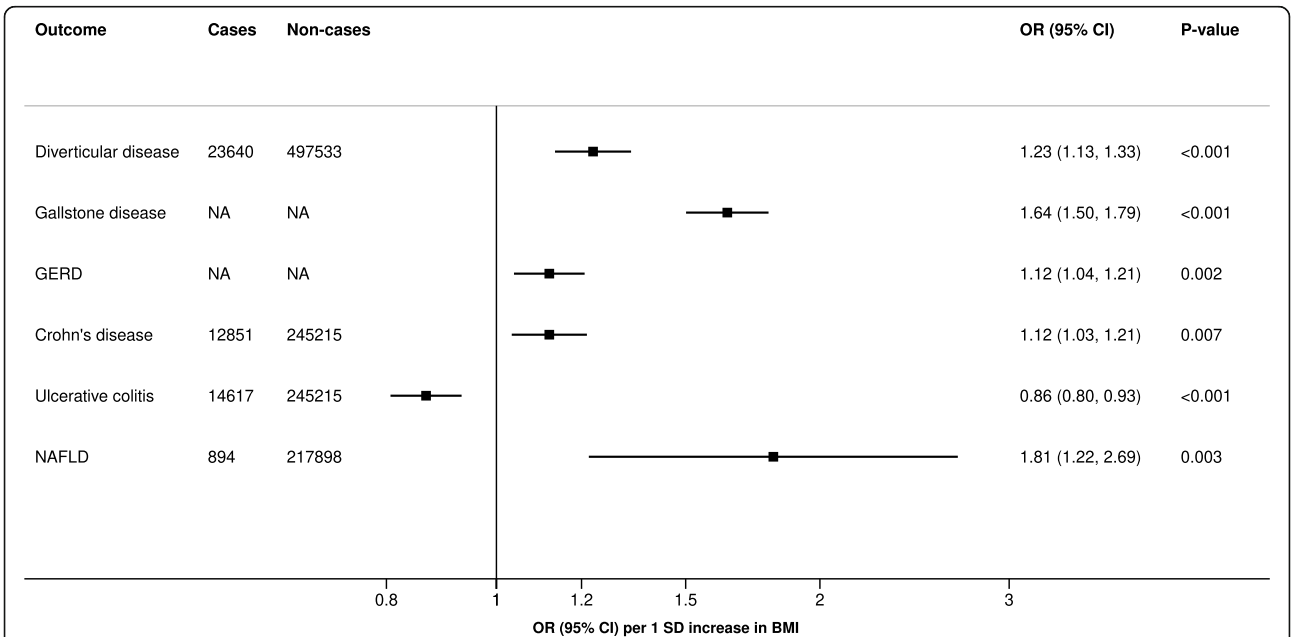

Fig. 3 Meta-analysis results for genetically predicted BMI in relation to diseases of the digestive system. Results are scaled per 1 *SD* increase of BMI. All analyses include individuals of European ancestry only. GERD gastroesophageal reflux disease, NA not available, NAFLD nonalcoholic fatty liver disease

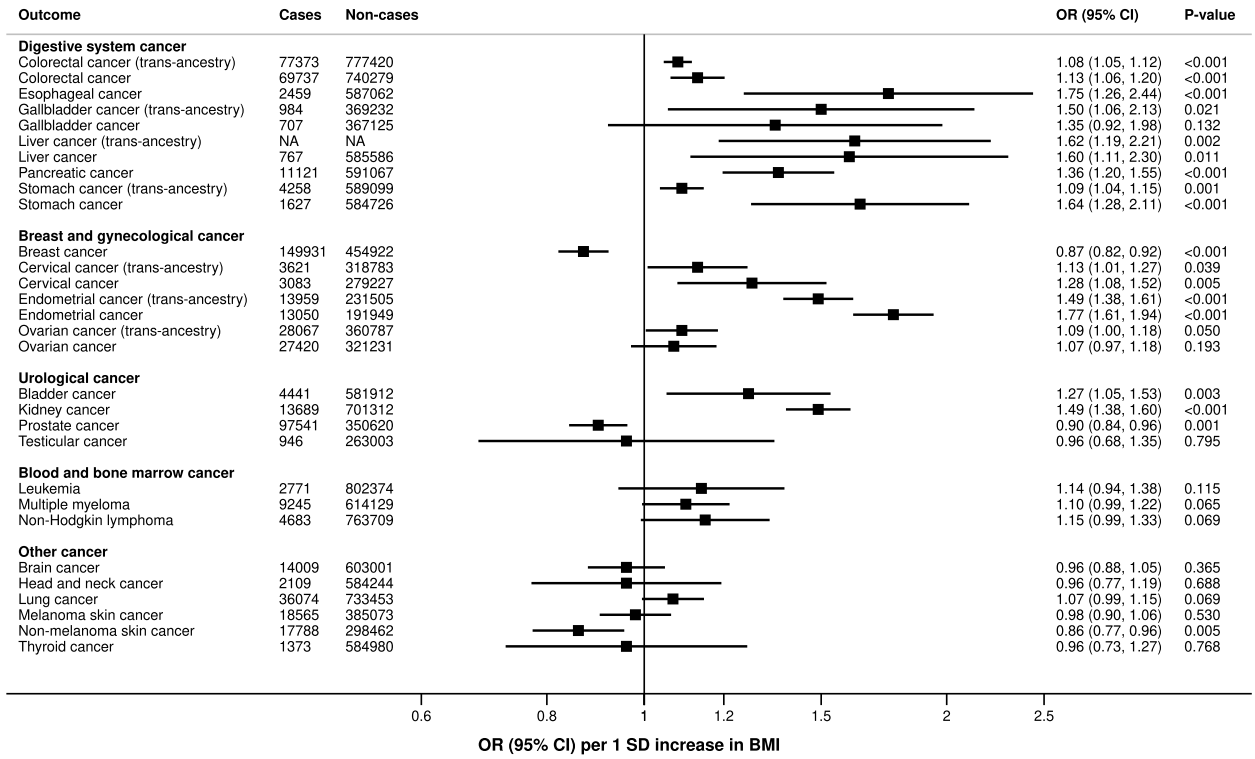

Fig. 4 Meta-analysis results for genetically predicted BMI in relation to neoplasms. Results are scaled per 1 *SD* increase of BMI. Analyses include individuals of European ancestry only if not otherwise indicated (i.e., trans-ancestry). NA not available

(Fig. 3, Additional file 1: Table S2). Results remained except for ovarian cancer when confining the study populations to individuals of European ancestry, but the magnitude of the association became weaker for colorectal cancer and stronger for stomach, endometrial, and cervical cancer (Additional file 1: Table S2).

Discussion

This contemporary meta-analysis of MR studies of genetically predicted BMI in relation to 56 chronic diseases provides evidence in support of causal associations of excess adiposity with increased risk of type 2 diabetes mellitus, 14 circulatory system diseases, asthma, chronic obstructive pulmonary disease, five digestive system diseases, three musculoskeletal system diseases, multiple sclerosis, and cancers of the digestive system (six cancer sites), uterus, kidney, and bladder. In contrast, MR evidence indicates that high BMI is associated with a decreased risk of breast, prostate, and non-melanoma skin cancer, Dupuytren's disease, and osteoporosis, and not likely associated with risk of Alzheimer disease, amyotrophic lateral sclerosis, or Parkinson's disease.

This meta-analysis of MR studies found consistent associations of higher genetically predicted BMI and increased risk of type 2 diabetes mellitus and cardiovascular diseases. However, conflicting results were found for adulthood BMI in relation to type 1 diabetes mellitus. The inconsistent results might be related to different ages at onset of type 1 diabetes mellitus in the UK Biobank and FinnGen populations or that genetic instruments for adulthood BMI rather than childhood BMI were used. An MR study of genetically predicted childhood BMI showed a positive association with childhood-onset (<17 years) type 1 diabetes mellitus (*OR* 1.32, *95% CI* 1.06–1.64 per *SD* score increase in BMI based on 32 SNPs) [62]. Excess adiposity may increase the risk of type 2 diabetes mellitus and cardiovascular diseases by increasing fasting glucose, insulin, and triglyceride levels; raising blood pressure; and promoting systemic inflammation [63–65]. An MR study based on consortia data found that the genetic association of BMI with risk of coronary artery disease, peripheral artery disease, and stroke was partly mediated by systolic blood pressure and type 2 diabetes mellitus, but not materially mediated by lipids or smoking [19].

Higher genetically predicted BMI was associated with increased risk of several diseases of the respiratory, digestive, and musculoskeletal systems, including asthma, gallbladder disease, diverticular disease, nonalcoholic fatty liver disease, gout, osteoarthritis, and rheumatoid arthritis. The associations may be related to an obesity-related reduction in lung volume (for asthma), joint

loading (for osteoarthritis), and alterations in microbiota composition, inflammatory mediators, and hormone levels. In contrast, higher genetically predicted BMI was associated with a modest lower risk of osteoporosis, possibly explained by mechanical stresses mediated through gravitational action. This finding confirms previous MR studies that have shown a positive association between genetically predicted BMI and bone mineral density [66, 67]. Genetically predicted BMI was also inversely associated with the risk of Dupuytren's disease in an MR study based on data from a genome-wide association study on this outcome [30]. The mechanism behind this association is unclear but might be related to lower testosterone levels with increasing BMI [30]. For the two inflammatory bowel diseases, the direction of the association with genetically predicted BMI differed for Crohn's disease (positive association) and ulcerative colitis (inverse association). A previous meta-analysis of observational studies found that BMI was positively associated with the risk of Crohn's disease but unrelated to ulcerative colitis [68]. Hence, the observed inverse association between genetically predicted BMI and ulcerative colitis in the present meta-analysis of two MR studies may be a spurious finding. In fact, the inverse association was only significant in the IBD consortium but not in the FinnGen consortium.

This meta-analysis of MR studies provided evidence that excess adiposity increases the risk of multiple sclerosis but not Alzheimer's disease, amyotrophic lateral sclerosis, or Parkinson's disease. If anything, a suggestive inverse association was observed between genetically predicted BMI and Parkinson's disease. This finding is consistent with the results of a previous meta-analysis that found that being underweight was associated with an increased risk of Parkinson's disease [69].

The opposite direction of the associations of genetically predicted BMI with different cancers suggests different causal pathways for BMI and various cancers. The increased risk of cancers of the digestive system, uterus, kidney, and bladder may be mediated by alterations in insulin signaling, growth factors, adipose tissue-derived inflammation, and hormone levels. Higher genetically predicted BMI has been shown to relate to lower serum testosterone levels [70], and testosterone levels are positively associated with risk of breast, prostate, and skin cancer [71, 72]. Thus, the observed inverse associations of genetically predicted BMI with these cancers might, at least in part, be explained by lower testosterone levels in overweight and obese individuals. In premenopausal women, high BMI may lower breast cancer risk via decreased estradiol levels [73].

Heterogeneity was observed between estimates from individual studies in analyses of genetically predicted BMI and several disease outcomes (e.g., diabetes, aortic valve stenosis, atrial fibrillation, hypertension, and stomach, endometrial, bladder, head and neck, and lung cancer). The detected heterogeneity was mainly caused by the different magnitude of the associations across studies and may be related to different genetic instruments used or to different study populations with different characteristics.

A strength of MR studies is that confounding and reverse causation bias are reduced as BMI is proxied by genetic variants that generally are not related to self-selected behaviors and environmental exposures and are not modified by disease development. The validity of MR findings relies on the absence of pleiotropy (i.e., where a genetic variant is associated with more than one phenotype). Researchers of most MR studies included in the meta-analysis performed sensitivity analyses and found limited evidence that the associations were biased by pleiotropy. Another limitation in MR studies of obesity and other harmful exposures in relation to late-onset diseases is competing risk bias, which is a potential type of survival bias. It cannot be ruled out that this bias might have affected the results in some of the studies. A further shortcoming is that most MR studies comprised individuals of European ancestry and therefore cannot infer causality of the role of excess adiposity in chronic diseases in non-European populations.

Conclusions

The totality of the evidence from published and de novo Mendelian randomization analyses supports a causal role of excess adiposity in a plurality of chronic diseases. Hence, continued efforts to reduce the prevalence of overweight and obesity are a major public health goal.

Abbreviations

BMI: Body mass index; *CI*: Confidence interval; MR: Mendelian randomization; *OR*: Odds ratio; *SD*: Standard deviation; SNPs: Single-nucleotide polymorphisms

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-021-02188-x.

Additional file 1: Tables S1-S2. Table S1 – Study quality assessment. Table S2 – Mendelian randomization studies included in the meta-analyses of genetically predicted body mass index in relation to diabetes mellitus, diseases of the circulatory, respiratory, digestive, musculoskeletal, and nervous systems, and neoplasms.

Acknowledgements

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Authors' contributions

SCL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; SCL did the literature search, extracted the data, performed the statistical analyses, and drafted the manuscript; SB reviewed the data extraction and critically revised

the manuscript for important intellectual content. Both authors contributed to data interpretation and approved the final version of the manuscript.

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Availability of data and materials
All the data supporting the conclusions of this article are included within the article and its supplementary files.

Declarations

Ethics approval and consent to participate
The analyses based on summary-level genetic data were approved by the Swedish Ethical Review Authority (ethics approval number 2019-02793).

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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