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Obesity as a causal risk factor for depression: Systematic review and meta-analysis of Mendelian Randomization studies and implications for population mental health

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A B S T R A C T

Background/objectives: Obesity has been associated with elevated risk of depression. If this association is causal, the increasing obesity prevalence might lead to worsening population mental health, but the strength of the causal effect has not been systematically evaluated.

Subjects/methods: The current study provides a systematic review and meta-analysis of studies examining associations between body mass index and depression using Mendelian randomization with multiple genetic variants as instruments for body mass index. We used this estimate to calculate the expected changes in prevalence of population psychological distress from the 1990s–2010s, which were compared with the empirically observed trends in psychological distress in the Health Survey for England (HSE) and U.S. National Health Interview Surveys (NHIS).

Results: Meta-analysis of 8 Mendelian randomization studies indicated an OR = 1.33 higher depression risk associated with obesity (95% confidence interval 1.19, 1.48). Between 15% and 20% of the participants of HSE and NHIS reported at least moderate psychological distress. The increase of obesity prevalence from the 1990s–2010s in HSE and NHIS would have led to a 0.6 percentage-point increase in population psychological distress.

Conclusions: Mendelian randomization studies suggest that obesity is a causal risk factor for elevated risk of depression. The increasing obesity rates may have modestly increased the prevalence of depressive symptoms in the general population. Mendelian randomization relies on methodological assumptions that may not always hold, so other quasi-experimental methods are needed to confirm the current conclusions.

1. Introduction

Individuals with obesity have an elevated risk of depression: a 55% higher odds risk was reported by a meta-analysis of longitudinal studies in which depression was assessed several years after obesity assessment among individuals with no depression at baseline (Luppino et al., 2010). If obesity does predispose to depression and other symptoms of psychological distress, including anxiety and somatic complaints (Goldberg and Blackwell, 1970; Kessler et al., 2003), the increasing rates of obesity might worsen overall population mental health the same way it has been shown to decrease population physical health (Wang et al., 2011). For example, in the 2018 World Happiness Report (Sachs et al., 2018), high obesity prevalence was cited as one of the possible health factors hindering improvements of happiness in the United States. However, the numbers underlying this public health perspective have not been worked out in detail. Are the mental health risks and obesity trends strong enough so that a doubling or tripling of obesity prevalence would be observed as a noticeable increase in the prevalence of psychological distress in the general population?

First, there is the question of causality. The association between body weight and depression could be confounded by many social, economic, or psychological characteristics, such as person's socioeconomic status, neighborhood characteristics, and social relationships that may influence both body weight and depressive symptoms (Markowitz et al., 2008). Mendelian randomization studies have explored whether obesity causes depression (Tyrrell et al., 2019; Jokela et al., 2012; Hartwig et al., 2016). These studies attempt to estimate unconfounded associations between exposure and outcome by relying only on the genetically determined variation in the exposure variable. This may help to remove confounding that arises from phenotypic correlations between exposure, outcome, and confounders (Gage et al., 2013). Using genetic variants as indicators for higher BMI, some of the Mendelian randomization studies have shown evidence of higher BMI causing depression (Tyrrell et al., 2019; Jokela et al., 2012; Hartwig et al., 2016). The evidence has not been consistent across all studies (Walter et al., 2015a; Hung et al., 2014; Kivimäki et al., 2011a), which may be related to differences in sample composition, measures of depression, genetic measures of BMI, or other methodological characteristics (Kivimäki et al., 2011a). Second, it remains to be determined how much the increasing obesity trends would increase population prevalence of depression over time, that is, whether

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the causal effect on depression is sufficiently strong to be detected at the population level.

In the current study, we evaluated the potential effects of increasing obesity rates on population prevalence of depression. First, we carried out a systematic review and meta-analysis of Mendelian randomization studies to derive feasible effect size estimates for obesity increasing the risk of depression. We then extrapolated these individual-level association to the population level by estimating how much the population prevalence of psychological distress—a broad measure of mental health that includes symptoms of depression but also anxiety and somatic complaints (Goldberg and Blackwell, 1970; Kessler et al., 2003)—would be expected to change based on changes in obesity prevalence, and how these compared to any observed trends in distress in the United States (from 1997 to 2016) and England (from 1991 to 2016).

2. Methods

2.1. Systematic review and meta-analysis of Mendelian randomization studies

We carried out a systematic review of studies using the following three eligibility criteria: the studies had to (Luppino et al., 2010) use Mendelian randomization, that is, instrumental variables regression with (Goldberg and Blackwell, 1970) multiple genetic variants as the instrument for BMI (Kessler et al., 2003) to predict individual differences in self-rated depressive symptoms or diagnosis of major depressive disorder. Thus, studies that used single genetic markers as the instrumental variable, or that used single self-rated items of depression as the outcome, were not considered because these study designs are likely to have limited reliability.

The literature review was performed with Scopus (scopus.com) in October 2021 by searching for the following keyword combinations in manuscript abstracts: (obesity OR bmi OR "body mass index") AND (depressi*) AND (mendelian OR instrumental OR causal OR polygenic). This yielded 539 documents that were screened independently by both authors. After reviewing the titles and abstracts of these articles, 516 were not considered eligible by either of the authors because these studies did not use instrumental-variables regression to study associations of BMI and depression.

Of the 23 studies that were retrieved for detailed inspection for eligibility, 15 were excluded because of the following reasons (Fig. 1):

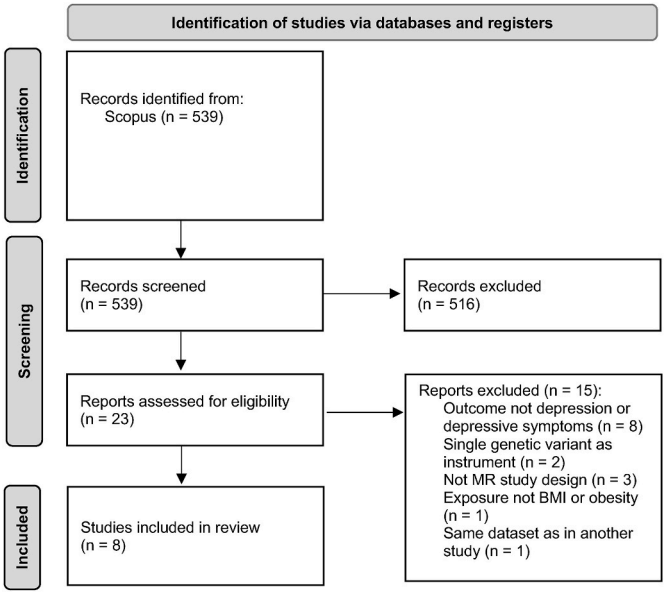

Fig. 1. Selection of the studies for the meta-analysis.

Two studies reported associations separately for depression (Walter et al., 2015a) and phobic anxiety (Walter et al., 2015b) from the same Nurses' Health Study, so we excluded the study of anxiety (Walter et al., 2015b) so as not to include the same data twice, and because we were primarily interested in depression as the outcome. One study (Samaan et al., 2015) was excluded because it only reported associations between the BMI genetic risk score and depression (OR = 1.01 per obesity-associated allele of a 21-SNP risk score, 95%CI = 0.99, 1.02) but not the gene–instrumented association between BMI and depression. Two studies from the UK Biobank cohort study were excluded: The first (Millard et al., 2019) reported associations between BMI and neuroticism-type personality characteristics separately by each questionnaire item (e.g., being nervous, a worrier, tense, and 'suffering from nerves'). High neuroticism is related to depression (Hakulinen et al., 2015), but the study was excluded because of the use of single personality items as the outcomes. The second study (Wootton et al., 2018) examined how BMI was related to five domains of life satisfaction (work, health, finances, friends, and family) and single-item scale of happiness. This study was also excluded because of the use of single-item questions. Two studies (Kivimäki et al., 2011b; Lawlor et al., 2011) used only single genes (*FTO* or *MC4R*) as instruments for BMI, which limits the validity of the instrument, and these two studies were therefore excluded.

One study (Bjørngaard et al., 2015) used offspring BMI as an instrument for parental BMI in predicting the parents' depression, anxiety, and suicide mortality, and another study (Hamer et al., 2016) used maternal BMI as an instrument for offspring in predicting the offspring's psychological distress. While the heritability of BMI (Jokela et al., 2016) implies that parent–offspring correlations might be considered as proxy genetic markers for the instrumental variable analysis, these two studies were excluded because they did not use genetic indicators as instruments for BMI. One study examined the instrumented association of depression on BMI (Mulugeta et al., 2019) and one study examined the associations of fat versus non-fat mass on depression risk in the UK Biobank study (Speed et al., 2019); these studies were outside the focus of the present review. Four studies were excluded because of the outcome not being depression: these studies reported associations between waist-hip ratio and schizophrenia (Peters et al., 2020); between BMI and symptoms of atypical depression (Pistis et al., 2021); between BMI and personality traits (Arumäe et al., 2021); and between health conditions and educational outcomes among children (Hughes et al., 2021). One study (Amin et al., 2020) reported MR analysis in two cohort studies (AddHealth and Health and Retirement Study) while another study (Willage, 2018) reported MR analysis only in one of these (AddHealth), so we excluded this latter study because of being based on the same dataset.

This study selection procedure left use with eight eligible studies to be included in the meta-analysis (Table 1). The first author collected the relevant information from the eligible studies (depression measure, genetic risk score, sample size, and the instrumented and non-instrumented associations between BMI and depression) and translated the reported effect sizes into odds ratios for the studies that used other effect size measures. The review or the protocol were not pre-registered, and there were no study sponsors involved in this study.

2.2. Empirical data

Health Survey for England is a nationally representative annual survey of health and lifestyles of the English people, started in 1991. Psychological distress was assessed with the 12-item General Health Questionnaire (GHQ; (Goldberg and Blackwell, 1970)). Each item is rated on a 4-point scale of how frequently the person has experienced depressive and somatic symptoms over the past few weeks (0 = not at all, 1 = no more than usual, 2 = rather more than usual, 3 = much more than usual) with 0 and 1 coded as 0, and 2 and 3 coded as 1. The dichotomously coded items are then summed together (range 0–12), and a score of $\geq$4 indicates moderate psychological distress, following

Table 1
Characteristics of the eight included Mendelian randomization studies in order of publication year.

Study (reference)	Genetic variants	Sample size	Measure of depression	Study design
Jokela et al., 2012 (Jokela et al., 2012)	31SNP	1731	Modified BDI (self-report)	One-sample
Hung et al., 2014 (Hung et al., 2014)	32SNP	3222	MDD (clinical interview)	One-sample
Walter et al., 2015 (Walter et al., 2015a)	31SNP*	6989	GDS (self-report)	One-sample
Hartwig et al., 2016 (Hartwig et al., 2016)	97SNP	339224	MDD (clinical interview; n = 18759)	Two-sample
van den Broek et al., 2018 (van den Broek et al., 2018)	78SNP	339224	MDD (interview), self-report (2 items), or health records (n = 161460)	Two-sample
Wray et al., 2018 (Wray et al., 2018)	85SNP	322154	MDD (interview), self-report (2 items), or health records (n = 480359)	Two-sample
Tyrrell et al., 2019 (Tyrrell et al., 2019)	73SNP	340,786	Self-reported depression history or treatment contact, and Hospital Episode Statistic records	One-sample
Amin et al., 2020 (Amin et al., 2020)	97SNP	AddHealth: 4928 HRS: 8867	AddHealth: 10-item CES-D (self-report) HRS: 8-item CES-D (self-report)	One-sample One-sample

Note: * Genetic instrument was the 32SNP score but with the FTO gene excluded. BDI = Beck Depression Inventory, MDD = Major Depressive Disorder, GDS = Geriatric Depression Scale, SNP = single nucleotide polymorphism, GWAS = genome-wide association study, CES-D = Center for Epidemiological Studies Depression, HRS = Health and Retirement Study.

previous studies with the HSE (Morris et al., 2017). Height and weight were measured by trained interviewers. Local research ethics committees approved all aspects of each survey, and all participants gave written informed consent. Only participants aged 18 or older were included, resulting in a total sample of 178,298 individuals. Sampling weights were used for survey years 2004 onwards, as sampling weights are not available for the earlier years.

U.S. National Health Interview Surveys are nationally representative surveys that have been carried out since 1957. The K6-scale (Kessler et al., 2003) of psychological distress has been included in the survey from 1997 onwards. The six items ask about feelings of nervousness, hopelessness, restlessness, sadness, worthless, and effortfulness occurring the past 30 days and are rated on a 5-point scale (0 = none of the time, 4 = all of the time) and summed together (range 0–24). In order to have more comparable estimates for population prevalence of psychological distress with the HSE, we used the previously suggested cut-off point of ≥5 for moderate psychological distress (Prochaska et al., 2012). Height and weight were self-reported by the participants. NHIS is approved by the Research Ethics Review Board of the National Center for Health Statistics and the U.S. Office of Management and Budget. All NHIS respondents provided verbal consent prior to participation. Only participants aged 18 or older were included, resulting in a total sample of 592,065 individuals. Sampling weights were used for all years.

2.3. Statistical analysis

The effect size estimates of Mendelian randomization studies were converted into odds ratios per 1SD difference in BMI. Standardized linear regression coefficients were converted (Borenstein et al., 2009) to log odds ratios by first converting them to Cohen's d with the formula $d = 2\beta/\text{sqrt}(1-\beta^2)$ and then to log odds ratios with the formula $\log(OR) = d\pi/\text{sqrt}$ (Kessler et al., 2003). Probit regression coefficients were converted into approximated logit coefficients by multiplying the probit coefficient by 1.6 (Gelman and Hill, 2007).

The effect sizes were then expressed as the approximated difference between individuals with vs. without obesity: The average difference in BMI between individuals with obesity (BMI>30) versus individuals without obesity (BMI≤30) was 10.5kg/m2 in NHIS and 9.1kg/m2 in HSE, and the standard deviations of BMI were 5.9kg/m2 and 4.9kg/m2. The difference between the groups with and without obesity was thus 1.78 and 1.86 in standard deviations of BMI (average of the two studies = 1.82). To provide odds ratios not only for 1SD difference in BMI but also for an approximated difference between having versus not having obesity, we report the odds ratios calculated for 1.82SD difference in BMI. The study estimates were pooled together using random-effect meta-analysis with the DerSimonian & Laird method (DerSimonian and Laird, 1986) which is one of the most common methods to estimate the summary effect size when assuming that some of the variation in effect sizes across studies is due to real differences between studies and not only sampling variability.

NHIS and HSE did not include repeated measures of depression, so we examined time trends in psychological distress. The projected psychological distress trends were calculated by first determining the distress prevalence among those without obesity at the beginning of the follow-up; then calculated the prevalence among those with obesity based on the estimated relative risk associated with obesity; and finally calculated the population distress prevalence as the weighted average of those with and without obesity. The projected psychological distress due to increasing obesity prevalence was then calculated based on the change in the prevalence of obesity over time, i.e., $D_{PY}=(1 - P_{OY}) \times D_{BL} + P_{OY} \times D_{BL} \times RR$, where D_{PY} is the population prevalence of distress in year Y, P_{OY} is the prevalence of obesity in year Y, D_{BL} is the baseline prevalence of distress among those without obesity, and RR is the relative risk of distress associated with obesity. This projection did not assume any time trend in psychological distress but allowed it only to change as a function of obesity prevalence. Non-parametric lowess curves were used to smooth the temporal trends in distress and obesity.

We also determined the population attributable fractions that indicated how much the risk of depression would decrease if obesity prevalence were zero as compared to its actual prevalence (Rockhill et al., 1998). These were calculated using the formula assuming no confounding (because of the assumptions of Mendelian randomization studies), that is, $PAF = [P \times (RR - 1)]/[P \times (RR - 1) + 1]$, where P is the proportion of participants with obesity and RR is the relative risk for depression risk associated with obesity. For calculating PAF the odds ratio (OR) derived from the meta-analysis was first converted into relative risk (RR) using the formula $RR = OR/(1 - p_0 + (p_0 \times OR))$ where p_0 is the baseline risk. The attributable fractions were calculated for the first and last years of the HSE and NHIS surveys.

3. Results

The characteristics of the included studies are shown in Table 1, and the original and transformed coefficients are shown in Table 2. A meta-analysis of the eight studies with genetic risk scores as instruments suggested an OR = 1.33 (95% confidence interval = 1.19, 1.48) increased risk of depression associated with obesity, that is, a 1.82SD difference in BMI (Fig. 2); the meta-analytic summary estimate for depression risk associated with 1SD difference in BMI was OR = 1.17 (1.10, 1.24). The three oldest studies had very wide confidence intervals that did overlap with the more precisely estimated observational associations.

Descriptive statistics of HSE and NSHIS are shown in Table 3. In HSE, obesity prevalence increased from 15% in 1991 to 27% in 2016. The population attributable fraction of obesity in psychological distress prevalence would have increased from 3.9% in 1991 to 6.8% in 2016.

Table 2
Effect size estimates in the eight included Mendelian randomization studies.

	Observational association	Mendelian randomization association	
		Original estimate	Converted to OR per 1SD BMI
Jokela et al., 2012 (Jokela et al., 2012)	B = 0.47 (0.32, 0.63) per BMI unit	B = 1.08 (0.11, 2.04) per BMI unit	3.78 (1.14, 22.2)[a]
Hung et al., 2014 (Hung et al., 2014)	Probit B = 0.05 (0.04, 0.06) per BMI unit	Probit B = −0.02 (−0.11, 0.07) per BMI unit	0.84 (0.39, 1.81)[b]
Walter et al., 2015 (Walter et al., 2015a)	B = 0.024 (0.020, 0.029) per BMI unit	B = −0.003 (−0.051, 0.045) per BMI unit	0.93 (0.29, 3.35)[c]
Hartwig et al., 2016 (Hartwig et al., 2016)	–	OR = 1.15 (0.92, 1.44) per 1SD BMI	–
van den Broek et al., 2018 (van den Broek et al., 2018)	–	Beta = 0.05 (0.01, 0.09) per 1SD BMI	1.20 (1.04, 1.39)
Wray et al., 2018 (Wray et al., 2018)	–	OR = 1.12 (1.08, 1.17) per 1SD BMI	–
Tyrrell et al., 2019 (Tyrrell et al., 2019)	OR = 1.16 (1.15, 1.17) per 1SD BMI	OR = 1.18 (1.09, 1.28) per 1SD BMI	–
Amin et al., 2020d (Amin et al., 2020)[d]	B = 0.002, SE = 0.001 B = 0.003, SE = 0.001	B = 0.003, SE = 0.003 B = 0.009, SE = 0.003	1.17 (0.84, 1.54) 1.50 (1.17, 1.86)

[a] SD(BMI) = 4.3, SD(Depression) = 13.5.
[b] SD(BMI) = 5.3.
[c] SD(BMI = 4.5), SD(Depression) = 0.64.
[d] Coefficients indicate the percentage point increase in the probability of depression. B = unstandardized coefficient, Beta = standardized coefficient.

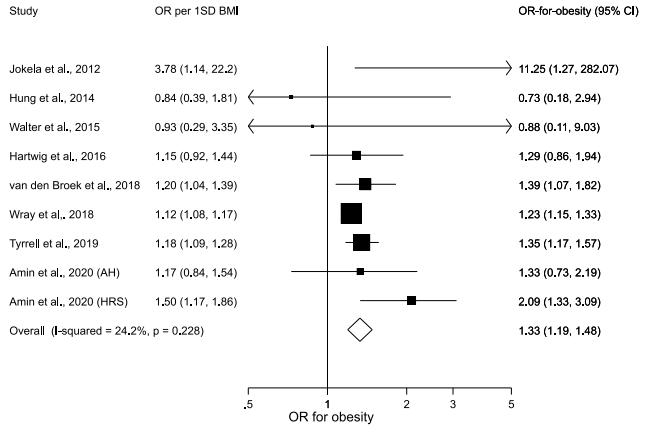

Fig. 2. Random-effect meta-analysis of eight Mendelian randomization studies of obesity as a causal risk factor for depression.

The prevalence of psychological distress among participant with BMI<30 in 1991 was 15.1%. Based on the increase in obesity from 15% in 1991 to 31% in 2016, and the RR = 1.27 higher risk among those with obesity (OR = 1.33 converted to RR = 1.27 when baseline risk was 15.1%), one would expect population psychological distress to have increased from 15.7% to 16.3% between 1991 and 2016. Fig. 3 shows the projected and observed trends in psychological distress. Distress prevalence decreased from 2003 to 2005 onwards, which may have partly been related to the use of sampling weights from 2004 onwards.

In NHIS, obesity prevalence increased from 19% in 1997 to 32% in 2016. The population attributable fraction of obesity in psychological distress prevalence would have increased from 4.5% in 1997 to 7.4% in 2016. The prevalence of psychological distress among participants with BMI<30 was 18.5% in 1997. Owing to increasing obesity prevalence, the population prevalence of psychological distress would have increased from 19.4% to 20.0% over the 20 years (OR = 1.33 converted to RR = 1.25 when baseline risk was 18.5%). Fig. 4 shows the projected and observed trends in psychological distress.

Table 3
Descriptive statistics of the HSE and NHIS.

	HSE	NHIS
Sex (%)		
Men	46.7	48.1
Women	53.3	51.9
Mean age (years)*	47.2	45.8
Age range[†]	18 to 102	18 to 85
Race/ethnicity (%)		
White	94.4	70.0
Black	1.8	11.6
Asian	3.1	3.1
Hispanic	–	13.1
Other	0.7	2.3
Education[‡] (%)		
Basic	27.6	15.5
Intermediate	43.7	28.0
Advanced	28.8	56.5
Psychological distress (%)	14.5	18.6
BMI>30kg/m2 (%)	21.8	26.6

Note: Values are sample-weighted frequencies unless otherwise noted. * Values are means. [†]Values indicate range of values. [‡]HSE: Basic = No qualifications; Intermediate = CSE or GCE; Advanced = Higher degree. NHIS: Basic = Less than high school; Intermediate = High school; Advanced = More than high school. HSE=Health Survey for England, NHIS=National Health Interview Survey, BMI=Body mass index.

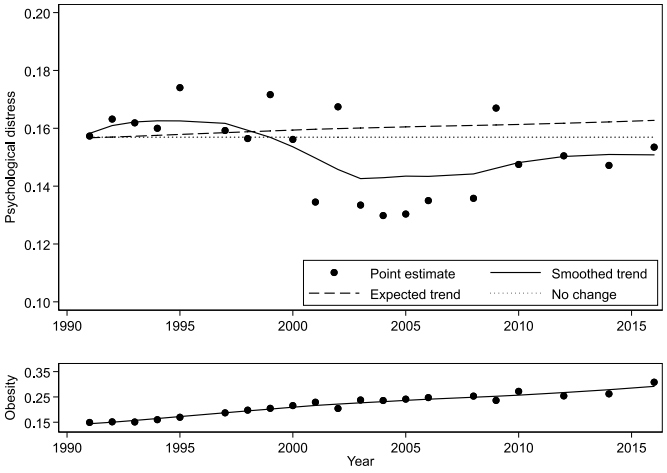

Fig. 3. Obesity and psychological distress in the Health Survey for England 1991–2016 (n = 178,298). In the upper panel, points indicate the prevalence of psychological distress by year, and the solid curve is the lowess smoother for their trend over time (bandwidth = 0.6). The dashed line is the projected trend in psychological distress based on the prevalence of obesity that year and the 1.33-fold odds of psychological distress among individuals with vs. without obesity (smoothed with lowess). The dotted line shows what the calculated psychological distress would have been with 1991 obesity prevalence. The lower panel shows the prevalence of obesity (trend smoothed with lowess).

4. Discussion

Evidence from Mendelian randomization studies suggests that obesity increases the risk of depression with an OR = 1.33 (CI = 1.19, 1.48). This is about two-thirds of the risk estimate suggested by a meta-

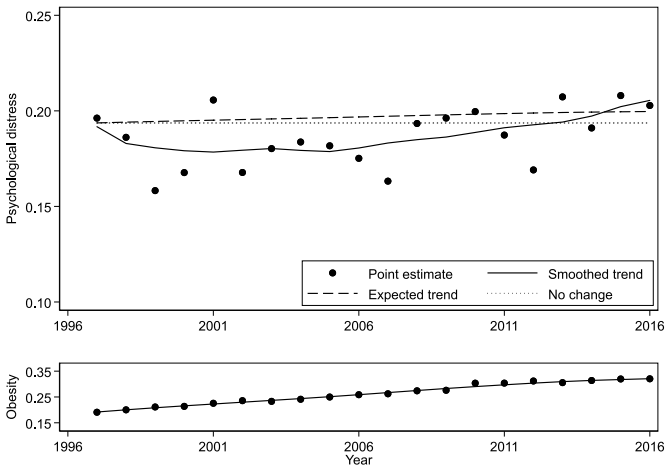

Fig. 4. Obesity and psychological distress in the U.S. National Health Interview Survey 1997–2016 (n = 592,065). In the upper panel, points indicate the prevalence of psychological distress by year, and the solid curve is the lowess smoother for their trend over time (bandwidth = 0.6). The dashed line is the projected trend in psychological distress based on the prevalence of obesity that year and the 1.33-fold odds of psychological distress among individuals with vs. without obesity (smoothed with lowess). The dotted line shows what the calculated psychological distress would have been with 1997 obesity prevalence. The lower panel shows the prevalence of obesity (trend smoothed with lowess).

analysis (Luppino et al., 2010) of longitudinal studies published in 2010 (OR = 1.55; 1.22, 1.98), implying that the longitudinal studies may have overestimated the causal risk of obesity for depression, but not dramatically so. The prevalence of obesity has doubled since the 1990s, which may have contributed to a half percentage-point increase in the population prevalence of psychological distress: an estimated increase from 15.7% to 16.3% in 1991–2016 England, and from 19.4% to 20.0% in 1997–2016 United States.

Mendelian randomization studies with small sample sizes or single genes as instruments for BMI have produced inconsistent results on the causal role of obesity in depression (Kivimäki et al., 2011a), which was also the case with the three smallest studies of the current meta-analysis. The estimates from published GWAS data and the UK Biobank were more consistent. The three studies that used summary GWAS data relied partly on the same sources of genetic information: all of them derived genetic BMI data from the Genetic Investigation of ANthropometric Traits consortium (GIANT; n = 339,224), while genetic depression data were derived from the Social Science Genetic Association Consortium (SSGAC; n = 161,460) by van den Broek et al. (Wray et al., 2018), from Psychiatric Genomics Consortium (PGC; n = 18,759) by Hartwig et al. (2016), and from seven cohorts including the PGC and UK Biobank (n = 480,359) by Wray et al. (2018), the UK Biobank also being used by Tyrrell et al. (2019). Because of the non-independence of the estimates, the confidence intervals of the meta-analytic summary estimate are probably too narrow. Our systematic review did not include the most recent genome-wide analysis of depression (Howard et al., 2019)—which is an updated analysis of genome-wide analysis that was included (Wray et al., 2018) in our meta-analysis—that also reported a Mendelian Randomization analysis of BMI and depression in their supplementary analysis. The inverse variance weighted estimate was β = 0.067 (SE = 0.041, p = 0.099), which would translate into an OR = 1.28, which is very close to the result of our meta-analysis (OR = 1.33).

Mendelian randomization studies mitigate the role of confounding by using genetic information as instrumental variables. These instrumented associations will be biased if the same genes influence both obesity and depression, or if the genetic risk associated with BMI also influences a third variable that, in turn, influences depression (Gage et al., 2013). There is some data to suggest genetic overlap between BMI and depressive symptoms (Jokela et al., 2016), in which case the assumptions of Mendelian randomization might not be met. Non-genetic instrumental variable analysis would be useful to validate the robustness of the Mendelian randomization estimates, although it may be difficult to find convincing social instrumental variables. Three of the studies in the meta-analysis included sensitivity analyses for pleiotropic effects and found the associations to be robust against pleiotropic effects (Tyrrell et al., 2019; Hartwig et al., 2016; van den Broek et al., 2018). One study (Tyrrell et al., 2019) included a test for negative controls (i.e., variables that are unlikely to be caused by higher BMI) that provided additional validity for the Mendelian randomization analysis. In all the included studies, the genetic risk score was a sufficiently strong instrument for Mendelian randomization analysis.

Obesity and depression share some common socioeconomic (Milaneschi et al., 2018), biological (Milaneschi et al., 2018), and psychological (Jokela et al., 2013) risk factors, and these common causes may inflate the associations between obesity and depression in observational studies. The mechanisms by which obesity increases depression are yet unknown. Biological factors, such as metabolic dysfunctions (Milaneschi et al., 2018; Jokela et al., 2014), may account for some of the increased risk. A Mendelian randomization study in the UK Biobank showed that higher fat mass was associated with higher depression risk whereas non-fat mass was not (Speed et al., 2019). Potential social risk factors include discrimination (Spahlholz et al., 2016) and poorer social outcomes related to obesity, for example, lower socioeconomic status (Han et al., 2011). Despite the broad range of plausible mechanisms, the empirical evidence connecting obesity, specific mediating mechanisms, and psychological distress remains sparse. The associations of obesity with depression may also depend on subtypes or specific symptoms of depression, as higher BMI has been associated particularly with symptoms of fatigue and lack of energy, which is partly explained by low-grade systemic inflammation (Frank et al., 2022). Obesity and depression have been reported to have higher genetic overlap especially among individuals with atypical features of depression, such as increased appetite and/or weight gain (Milanechi et al., 2017; Badini et al., 2022).

The causal effect of obesity on depression does not exclude the possibility that depression would also cause obesity. Observational studies have suggested some evidence for a bidirectional association, that is, that psychological distress might also increase BMI (Kivimäki et al., 2009). One study with maternal psychological distress as an instrument for offspring psychological distress also concluded that psychological distress would influence body weight and not the other way around (Hamer et al., 2016). A Mendelian randomization study with a 42-SNP risk score for depression found no evidence for a causal effect of depression on obesity (Wray et al., 2018) whereas another Mendelian randomization with 44-SNP risk score for depression did find evidence for depression increasing BMI (Mulugeta et al., 2019). Given that the polygenic scores of depression still account for a very small proportion of variance in depression (Howard et al., 2019), Mendelian randomization studies alone are not sufficient for determining the bidirectional causal associations between obesity and depression.

In the empirical analysis of population trends, we examined trends of psychological distress as proxy measures for depressive symptoms, because NHIS and HSE did not include repeated measures of depression. The overlap of these measures with symptoms of depression is considerable. For instance, the K6 scale (Goldberg and Blackwell, 1970) asks about symptoms of nervousness, hopelessness, restlessness, sadness, worthless, and effortfulness. There were no clear trends in psychological distress over time so it was not possible to determine how much obesity might have explained any upward secular trend in psychological distress. The lack of robust secular trends in the prevalence of psychological distress has been noted in other analyses as well (Mojtabai and Jorm, 2015; Baxter et al., 2014). The population-level projections should therefore be considered only as illustrations of how the estimated increase in distress due to increasing obesity rate compares to the overall

variation in psychological distress, especially as BMI is only one of the many risk factors associated with psychological distress risk; we would not expect changes in average BMI to be a major driver of changes in psychological distress.

The present findings need to be considered within some limitations. First, we only focused on depression, but other indicators of mental health should be considered when evaluating the overall mental health burden of obesity. For example, obesity is associated with lower rather than higher rates of suicide (Klinitzke et al., 2013) so an increase in depression due to obesity may not translate into higher suicide rates. Second, the causality needs to be demonstrated with other experimental or quasi-experimental study designs because the instrumental-variable assumptions of Mendelian randomization may not always hold. Third, the Mendelian randomization studies have not examined whether the causal effect is observed in different subpopulations, so it is unclear whether the findings generalize across, say, different ethnic or socio-economic groups.

In sum, obesity seems to be a causal risk factor for depression, increasing its odds by 33%. Between 15% and 20% of the general population are estimated to suffer from at least moderate psychological distress. The doubling of obesity prevalence from the 1990s–2010s would have increased this prevalence by one-half percentage points.

Author contributions

MJ and ML screened potentially eligible studies, contributed to writing the report, and interpreting results. MJ was responsible for extracting and analysing data, and writing the first draft. ML provided feedback on the draft.

Declaration of competing interest

The author has no conflict of interests.

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