

**Common mental disorder and obesity — Insight from 4 repeat measures over 19 years:
The prospective Whitehall II cohort study**

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Abstract

Objective: To examine potential reciprocal associations between common mental disorders and obesity, and to assess whether there are dose-response relationships.

Design: Prospective cohort study with four measures of common mental disorders and obesity over 19 years (Whitehall II study).

Settings: Civil service departments in London.

Participants: 4363 adults (28% female, mean age 44 years at baseline).

Main outcome: Common mental disorder defined as General Health Questionnaire 'caseness'; overweight and obesity based on World Health Organization definitions.

Results: In models adjusted for age, sex and body mass index at baseline, odds ratios for obesity at the fourth screening were 1.33 (95% confidence interval 1.00 to 1.77), 1.64 (1.13 to 2.36) and 2.01 (1.21 to 3.34) for participants with common mental disorder at one, two or three preceding screenings compared to individuals free from common mental disorder ($p_{\text{trend}} < 0.0001$). The corresponding mean differences in body mass index at the last screening were 0.20, 0.31, 0.50 kg/m², respectively ($p_{\text{trend}} < 0.0001$). These associations remained after adjustments for baseline characteristics related to mental health and the exclusion of participants who were obese at baseline. In addition, obesity predicted future risk of common mental disorder, again with evidence of a dose-response relationship ($p_{\text{trend}} = 0.02$, multivariable model). However, this association was lost when individuals with common mental disorder at baseline were excluded ($p_{\text{trend}} = 0.33$).

Conclusions: These findings suggest that in British adults the direction of association between common mental disorders and obesity is from common mental disorder to increased future risk of obesity. This association is cumulative such that individuals with chronic or repeat episodes of common mental disorder are particularly at risk of weight gain.

INTRODUCTION

Common mental disorders, such as depression and anxiety, have been hypothesised to increase risk of obesity, but evidence is inconclusive.¹ Some studies show higher obesity rates in individuals with mental health problems,²⁻⁵ others report no association,⁶ or even a reverse effect, although the latter has largely been seen in subgroups that offer limited generalisability.^{4,7} As the development of obesity has a relatively long induction period, chronic or recurrent rather than transient mental disorder, is a more plausible cause. However, previous studies have typically measured common mental disorder at only one point in time.

There are also a series of studies that have explored the opposite causal direction; that is, obesity as a risk factor for future mental disorder. Again, the results from these studies have been contradictory:⁸ some find that individuals with greater body mass index experience an increased risk of depression and anxiety disorders,^{6,9,10} others report no association of obesity with these outcomes¹¹ while another group of studies have reported negative associations (greater obesity being associated with reduced risk of future mental health problems and suicide).^{12,13}

Several mechanisms could explain these two causal directions. The associations between obesity and common mental disorder may be context specific, depending on, for example, attitudes towards body size and mental ill health, such that the nature of the associations differs in different populations. That is, in societies where obesity is stigmatised this may lead to increased risk of anxiety and depression.¹⁴ On the other hand, stress and common mental disorders themselves are associated with disordered eating which could influence future changes in adiposity,^{15,16} and commonly used treatments for depression have known side-effects that also could result in weight gain.¹⁷

Given the public health importance of the increasing rates of both obesity and common mental disorder,^{18,19} understanding the nature of the association between these two

conditions is crucial and could potentially inform prevention and treatment. Prospective studies with repeat measurements of both common mental disorder and obesity offer a unique opportunity for in-depth study of this issue but are rare. Such studies have the capacity to explore the possible reciprocal nature of these associations, and determine whether there is a dose-response (cumulative) effect in either direction. The present study takes advantage of four waves of medical screening from the Whitehall II study of British government employees to determine the direction and possible dose-response nature of the association between common mental disorder and obesity.

METHODS

Study population

The target population of the British Whitehall II study was all London-based office staff, aged 35-55, working in 20 civil service (government) departments at study baseline in 1985-1988.²⁰ With a response of 73%, the baseline cohort consisted of 10,308 employees (6,895 men and 3,413 women).

Design

Since the first medical examination (Phase 1 1985-1988), follow-up screenings with a medical examination have taken place on 3 occasions over a 19-year period: Phase 3 (1991-1993), Phase 5 (1997-1999) and Phase 7 (2003-2004). All these phases included a standardised assessment of common mental disorder (General Health Questionnaire (GHQ); described below) and direct measurement of weight and height from which body mass index (BMI) was derived.

Baseline characteristics

Demographic characteristics, behavioural risk factors and chronic health conditions measured were: age, ethnicity (Caucasian vs non-Caucasian), marital status (married or co-habiting vs other), socioeconomic position (high, intermediate, low derived from civil service employment grade), smoking (never smoker, ex-smoker, 1-10, 11-20 or >20 cigarettes per day), alcohol consumption (0, 1-21 and >21 units of alcohol per week for men; 0, 1-14 and >14 units for women), physical activity (vigorous, moderate, mild), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), total cholesterol (mmol/L), diabetes (self-reported), and coronary heart disease (CHD).²⁰ CHD was defined by using the Multinational Monitoring of trends and determinants in cardiovascular disease (MONICA) criteria,²¹ using responses to questions about chest pain and physician diagnoses, examination of medical records and electrocardiography findings. We considered these variables as potential confounders or mediating factors in the association between common mental disorder and obesity.

Common mental disorder

We assessed common mental disorders using the self-administered 30-item GHQ,²² a screening instrument designed for community settings. It has been validated against standardised clinical interviews, has shown high reliability and been widely used in large population-based surveys and trials and demonstrated high predictive validity such that people classified as 'cases' have elevated mortality rates relative to non-cases.²³

Each GHQ item enquires about a specific symptom. Response categories are scored either 1 or 0 to indicate whether the symptom is present or not. On the basis of receiver operating characteristics and previous studies, we defined people with a total score of 5 or more as GHQ cases and those scoring 0-4 as non-cases.²⁴ In the present study, in which GHQ scores were validated against a Clinical Interview Schedule, sensitivity (73%) and specificity

(78%) measures indicate this definition of ‘caseness’ to be acceptable.²⁴ Given that we explored bi-directional associations between common mental disorders and obesity, GHQ-caseness (and obesity) could be considered an exposure variable or an outcome.

Obesity and overweight

BMI was calculated as weight (kilograms)/ height (metres) squared. Following the World Health Organization definition, participants with BMI 25 to 29.9 kg/m² were considered overweight and those with BMI ≥ 30 kg/m² obese.²⁵ Weight was measured in underwear to the nearest 0.1 kg on Soehnle electronic scales. Height was measured in bare feet to the nearest 1 mm using a stadiometer with the participant standing erect with head in the Frankfort plane. Repeatability of the weight and height measurements over 1 month (ie between-subject variability/total (between + within subject) variability), undertaken on 306 participants, was 0.99 at the Phase 7 screening.

Statistical analysis

First, to explore potential selection bias, we compared baseline characteristics between participants included in the analytic sample and those excluded by using χ^2 -test (categorical variables) or t-test (continuous traits). In the analytic sample, two sets of analyses were then run to examine the dose-response pattern and direction of the association between common mental disorders and obesity.

Analyses 1: Common mental disorder as a risk factor for subsequent overweight and obesity. Participants were divided into 4 groups based on the number of times they were GHQ-cases at the three first measurement phases (Phases 1, 3 and 5). We summarized the association between occurrence of GHQ-caseness and BMI category [<25 (normal weight), 25-29.9 (overweight), ≥ 30 (obese) kg/m²] at the end of follow-up (phase 7) using multinomial

logistic regression analysis. This method enabled us to examine whether the association between GHQ-caseness and obesity differed from that for overweight. The multinomial regression analysis produced odds ratios for being overweight and obese at the last screening (both compared to a reference of normal weight) for participants who had been GHQ cases 0, 1, 2 or 3 times at the preceding screenings.

Analyses 2: Obesity as a risk factor for future common mental disorder. In these analyses, participants were divided into 4 groups based on the number of times they were obese at the first three measurement phases (0, 1, 2 or 3 times). We examined the associations between occurrence of obesity and GHQ-caseness at the end of follow-up (Phase 7) using logistic regression analysis.

In both Analysis 1 and 2, there was no evidence of sex or ethnic differences in any of the associations between GHQ-caseness and obesity ($p = 0.34 - 0.98$ for all sex and ethnicity interactions), thus the data for men and women and for ethnic groups were pooled and appropriate adjustments made in subsequent analyses. In both analyses, regression estimates and accompanying 95% confidence intervals (CI) were first estimated without adjustments, then with control for age, sex and baseline BMI category (Analyses 1) or baseline GHQ-caseness (Analyses 2). Further adjustments took into account all baseline characteristics to examine other potential confounding or mediated effects.

Sensitivity analyses. To test the robustness of our findings, we ran 3 types of sensitivity analyses. First, to examine temporality in the associations, we focused on subgroups, excluding from the analyses individuals who were obese or overweight at baseline (Analysis 1) and individuals who were GHQ-cases at baseline (Analysis 2). Second, to examine whether the association between GHQ-caseness and subsequent obesity was sensitive to the pre-defined BMI cut-offs used, we repeated Analyses 1 using linear regression analysis with continuous BMI (rather than BMI category) as the outcome. Third, to further

explore the impact of selection bias due to missing data, we used multiple multivariate imputation and repeated the analyses based on an imputed sample of all participants who were alive during the whole study period (n=9,775)(see online Annex 1)

All analyses were performed with Stata 10.1 statistical software for Windows, StataCorp LP, Texas, USA.

RESULTS

Sample selection and sample characteristics

Sample selection is shown in Figure 1. Of the 10,308 participants at phase 1, 10,175 (98.7%) had complete data on weight, height and GHQ-caseness. At the following phase, these data were available for 7,819 participants (77.7% of the phase 1 participants who had complete data at phase 1 and were alive at phase 3). At phases 5 and 7, the corresponding figures were 5,069 (65.7% of those alive at phase 5) and 4,363 (87.5% of those alive at phase 7), respectively. Our main analysis is based on those 4,363 participants (3,122 men and 1,241 women) who had complete data on common mental disorders, weight and height at baseline and all follow-up measurements (44.6% of the baseline cohort after excluding the 533 participants who died during follow-up).

The mean age of the included participants with complete data was 44.0 years and 26.7% met the criteria for GHQ-caseness at Phase 1 (table 1). A comparison of individuals included in the analyses with individuals excluded because of loss to follow-up or missing data revealed modest differences, although statistical significance was often reached because of the large study numbers. Participants included were 0.4 years younger, less often obese, had 0.5 kg/m² lower BMI and a somewhat more favourable risk factor profile than excluded participants. There were no differences in GHQ-case prevalence between the two groups,

although the proportion of individuals on psychotropic pharmacologic treatment was 1.0% lower among the participants than among the excluded.

Analyses 1: Common mental disorder as a risk factor for subsequent overweight and obesity

The mean follow-up from phase 1 to phase 7 was 16.5 years (range: 14.6 to 18.8) and the mean observation period over the three first screenings was 11.0 years (range: 9.1 to 13.3). Of the participants included in the analysis, 2,379 (54.5%) never met the definition for GHQ-caseness across the first three screenings, 1,159 (26.6%) were GHQ-cases at one, 585 (13.4%) at two and 240 (5.5%) at all three screenings.

Occurrence of GHQ-caseness was associated with subsequent obesity (compared with being of normal weight) in a dose response manner: unadjusted odds ratios were 1.11 (95% CI 0.90 to 1.36), 1.27 (0.98 to 1.66) and 1.56 (1.10 to 2.21) for GHQ-caseness at one, two or three screenings compared to participants who were case free ($p_{\text{trend}} = 0.004$). There was no robust association between GHQ-caseness at the first three screenings and subsequent overweight in the unadjusted analysis ($p_{\text{trend}} = 0.83$, data not shown). Table 2 presents multivariate models for these associations among the 4154 participants with complete data. The dose-response association with obesity was robust to adjustment for a wide range of potential covariates: age, sex, baseline BMI category (Model A), ethnicity, marital status, socioeconomic position, smoking, alcohol intake, physical activity, blood pressure, total cholesterol, diabetes, CHD, and use of psychotropic drugs (Model B).

Analyses 2: Obesity as a risk factor for future common mental disorder

Of the 4,363 participants, 3,727 (85.4%) were not obese at any of the three phases; 291 (6.7%) were obese once, 175 (4.0%) twice and 170 (3.9%) on three occasions. The odds ratios

of GHQ caseness at phase 7 increased with the number of times participants were obese. Compared to non-obese individuals the odds ratios in unadjusted analysis for those obese one, two or three times were 1.29 (95% CI 0.97 to 1.71), 1.35 (0.95 to 1.93) and 1.45 (1.02 to 2.06), respectively ($p_{\text{trend}}=0.004$). However, as shown in multivariate models (table 3), all the odds ratios between obesity categories and subsequent GHQ-caseness were non-significant when adjusted for covariables although the overall trend remained ($p_{\text{trend}}=0.01$ and 0.02 in Models A and B respectively).

Sensitivity analyses

We repeated Analysis 1 and 2 in subgroups to further study the temporal order between GHQ-caseness and obesity (table 4). The dose-response relationship between occurrence of GHQ-caseness and subsequent obesity remained after excluding participants who were obese at phase 1 ($n=214$, $p_{\text{trend}}<0.0001$) and those who were overweight ($n=1,356$, $p_{\text{trend}}=0.03$). By contrast, in the analysis to test the reverse direction the association between occurrence of obesity and subsequent GHQ-caseness was lost when participants defined as GHQ-cases at phase 1 ($n=1,164$) were excluded from the analysis ($p_{\text{trend}}=0.33$).

Further testing dealt with the association between GHQ-caseness and subsequent obesity. Results from the analysis with continuous BMI at phase 7 as the outcome were consistent with the main findings using BMI categories. In models adjusted for age, sex and BMI at baseline, mean differences in BMI at the fourth study phase were 0.20 (95% confidence interval 0.02 to 0.37), 0.31 (0.09 to 0.54) and 0.50 (0.17 to 0.83) kg/m^2 for those defined as GHQ-cases one, two or three times relative to those who were never defined as cases ($p_{\text{trend}}<0.0001$, $n=4,154$). After adjusting for all baseline covariates and excluding obese participants at phase 1, the corresponding mean differences were 0.19 (0.03 to 0.35), 0.38

(0.16 to 0.59) and 0.40 (0.09 to 0.72), respectively, again clearly supporting a dose-response association ($p_{\text{trend}} < 0.0001$, $n=3,957$).

We used multiple imputation to repeat the analyses reported in table 2 (common mental disorder as a predictor of obesity) based on all participants alive at phase 7, a total of 9,775 persons (online Annex 1). The dose-response association between GHQ caseness and subsequent obesity was very similar to that obtained in the complete case analysis (table 2). Occurrence of GHQ-caseness was also associated with subsequent overweight ($p_{\text{trend}}=0.02$) in these analyses.

DISCUSSION

Principal findings

Findings from this well-characterized occupational cohort of over 4000 men and women provide evidence that common mental disorder may be a risk factor for future obesity.

Additionally, there was evidence that this effect appears to be cumulative. Thus, the odds ratio of being obese at the fourth and final screening were two times higher for participants with common mental disorder at all three preceding screenings compared to those who were disorder-free at all previous screenings. There was evidence of a dose-response in the association of common mental disorder with obesity, such that those who experienced more episodes of the disorder had greater risk of obesity. This dose-response association was independent of a wide range of mental-health-related characteristics at baseline which may be associated with both obesity and common mental disorder, including initial BMI, age, sex, ethnicity, marital status, socioeconomic position, smoking, alcohol intake, physical activity, blood pressure, cholesterol, diabetes, coronary heart disease, and use of psychotropic drugs. A similar pattern of associations was observed when we used BMI as a continuous variable.

When we examined the association in the opposite direction (i.e. obesity as a risk factor for

common mental disorder) we also found a dose-response association. However, when participants with common mental disorder at baseline were removed there was no association of obesity with future risk of common mental disorder. These results suggest that in this cohort of British adults there is a temporal sequence from mental disorder to obesity.

Strengths and weaknesses

Randomised controlled trials are important for the demonstration of causal effects but in this case, where the interest is in the association between long-term mental disorder and obesity, they may not be feasible. In such cases, observational data, like ours, provide the best available source of evidence, although they can never provide complete proof of causality. For example, even though adjustment for a wide range of covariates had little effect on our estimates of association, the possibility of residual confounding cannot be excluded in observational research.

Despite a high survey response (range: 66% to 88%) at the successive data collection phases, loss-to-follow-up accumulated over the extended time period, as is inevitable in all long term prospective studies. However, associations were similar in our complete case analyses and analyses based on multivariate multiple imputation datasets (Annex 1).

Multivariate multiple imputation, in common with other procedures for dealing with missing data, assumes similarity in the associations between the exposure and outcome in those with and without missing data. This assumption cannot be tested in any real dataset, but among those with missing data, missingness would have to be more common for individuals with both mental disorder and low BMI or with both an absence of mental disorder and high BMI to create a spurious association between common mental disorder and obesity. We cannot see any reason why this should be the case.

Our findings are based on data obtained using a validated standard questionnaire measure of common mental disorders and by direct measurements of height and weight. In community-based samples mental health problems are frequently characterised by shifting patterns of symptoms that resist the precise classification used for clinical populations and capture variations in mental health rather than diagnosed mental illnesses.^{26 27} **In order to characterise long-term mental health problems, we calculated the number of times that each participant met the criteria for common mental disorder over the first three phases of the study. In doing so, equal weight was given to data from each phase since the purpose was to estimate each participant's propensity for common mental disorder over the whole period rather than to estimate proximal or distal effects of disorder on obesity.**

Two-thirds of our cohort were white-collar men, potentially reducing the generalisability of our findings. Furthermore, occupational groups are, by their very nature, healthier than their general population, and therefore the range of scores on the GHQ test and BMI range might be narrower. This being the case, the associations reported herein will, if anything, be an underestimate of the associations in the general population, which includes those not in employment.

Comparison with previous studies

We are not aware of any other study that has four repeat measurements of common mental disorders and direct assessment of weight and height, over an extended follow-up period. The present analyses therefore make a unique contribution to this area of research. Our findings are in agreement with a recent longitudinal study of elderly people showing weight gain to be more common among individuals with depression symptoms than among those who were symptom-free.⁵ Our results are also consistent with those from another cohort that used two sets of measurements to explore the bidirectional association between depression and type 2

diabetes, a condition associated with raised BMI.¹⁰ In that study baseline depressive symptoms were associated with increased risk of type 2 diabetes at the second follow-up (two years later) after removal of those with diabetes at baseline and adjustment for a wide range of potential confounding factors. Given that obesity is the major risk factor for type 2 diabetes, this association would be anticipated from our results, although the association in that study persisted even after adjustment for BMI, suggesting that it may not be entirely mediated via adiposity. Furthermore, in that cohort¹⁰ study members with treated type 2 diabetes at baseline were at increased risk of depressive symptoms two years later, again after removal of those with depressive symptoms at baseline and adjustment for a wide-range of potential confounding factors including BMI. Interestingly, impaired fasting glucose and untreated diabetes at baseline were not associated with future risk of depressive symptoms two years later, raising the possibility that the association of treated diabetes with future symptoms may be related to diagnosis with a chronic disease (or the treatment in terms of medication and dietary restrictions) rather than obesity or other specific biological mechanisms underlying diabetes. This possibility is consistent with our findings suggesting no real association between obesity and subsequent common mental disorder.

Meaning of the study

The two sets of analyses provide evidence that in this population of British middle-aged adults common mental disorder is predictive of subsequent weight gain and obesity. Evidence of a dose-response relationship also suggests that individuals with chronic or repeat episodes of common mental disorder are particularly at risk of subsequent obesity. By contrast, our findings do not suggest that obesity leads to common mental disorders in this population as the association between the two was attenuated when study members who were GHQ-cases at baseline were removed from the analysis.

There are a series of plausible explanations for the observation that persistent common mental disorder is a risk factor for obesity. First, common mental disorders are associated with eating disorders, both over- and under-consumption, which could influence future changes in adiposity.^{15 16} Second, physical inactivity, a major contributing factor to obesity, is more prevalent among people with mental health problems and some randomised controlled trials suggest exercise may reduce depressive symptoms among those with a diagnosis of depression, though in high quality trials the effect is close to the null.²⁸ Third, commonly used pharmacologic treatments for mental disorders have known side-effects that may result in weight gain (tricyclic antidepressants), weight loss (selective serotonin reuptake inhibitors, SSRIs) or both (short- and long-term effects of SSRIs).^{17 29} Fourth, biological factors, such as dysregulation of the hypothalamic-pituitary-adrenocortical (HPA) axis, may strengthen the link between mental disorders and obesity.³⁰ For example, there is some evidence of abnormal hormone concentration of the HPA axis among obese people with co-existing depressive symptoms.³¹ All these mechanisms are likely to increase obesity risk in a dose-response fashion such that single episodes of, for example hormonal dysregulation, would be less likely to increase risk than two, three or more repeated episodes or than a chronic continuous disorder.

Unanswered questions

Further longitudinal research is now needed to confirm the generalisability of the present findings to wider populations; to identify major social, behavioural and biological mechanisms underlying the observed associations; **to identify the time lag between exposure and outcome**; and to determine whether our findings are directly transferable to patients meeting the Diagnostic and Statistical Manual of Mental Disorders or International Classification of Diseases criteria for specific mental disorders, such as depression. Long-

term follow-up of randomised controlled trials for the prevention of common mental disorder in vulnerable groups that look at obesity as an outcome would be helpful in proving causality, as would Mendelian randomization studies which showed that genetic variants robustly associated with common mental disorder are also related to obesity. If the observed associations are causal, our findings have important implications for prevention and treatment. As obesity is a major risk factor for various chronic conditions and premature death,¹⁹ an increased risk of obesity induced by mental health problems should be taken into account in the treatment of persistent common mental disorders.

WHAT IS ALREADY KNOWN

It is unclear whether common mental disorders predict obesity or whether obesity predicts common mental disorders.

Few studies have the repeat measures necessary to understand the nature of the association.

WHAT THIS STUDY ADDS

Common mental disorder predicted subsequent obesity in a cohort of 4000 men and women over a 19-year follow-up period.

Weight gain and the risk of obesity increased in a dose-response fashion with the number of episodes of common mental disorder.

There was little evidence to suggest that obesity was a risk factor for subsequent common mental disorder in people with no pre-existing mental disorder.

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Contributors: All authors jointly designed the hypothesis, analysed and interpreted the data, and wrote the paper. MK is guarantor for the paper.

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Ethical approval: Ethical approval for the Whitehall II study was obtained from the University College London Medical School committee on the ethics of human research.

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References

1. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. *J Clin Psychiatry* 2004;65(5):634-51, quiz 730.
2. Goodman E, Whitaker RC. A prospective study of the role of depression in the development and persistence of adolescent obesity. *Pediatrics* 2002;110(3):497-504.
3. Weil E, Wachterman M, McCarthy EP, Davis RB, O'Day B, Iezzoni LI, et al. Obesity among adults with disabling conditions. *Jama* 2002;288(10):1265-8.
4. Stunkard AJ, Faith MS, Allison KC. Depression and obesity. *Biol Psychiatry* 2003;54(3):330-7.
5. Vogelzangs N, Kritchevsky SB, Beekman AT, Newman AB, Satterfield S, Simonsick EM, et al. Depressive symptoms and change in abdominal obesity in older persons. *Arch Gen Psychiatry* 2008;65(12):1386-93.
6. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes Relat Metab Disord* 2003;27(4):514-21.
7. Heo M, Pietrobelli A, Fontaine KR, Sirey JA, Faith MS. Depressive mood and obesity in US adults: comparison and moderation by sex, age, and race. *Int J Obes (Lond)* 2006;30(3):513-9.
8. Atlantis E, Baker M. Obesity effects on depression: systematic review of epidemiological studies. *Int J Obes (Lond)* 2008;32(6):881-91.
9. Farmer A, Korszun A, Owen MJ, Craddock N, Jones L, Jones I, et al. Medical disorders in people with recurrent depression. *Br J Psychiatry* 2008;192(5):351-5.
10. Golden SH, Lazo M, Carnethon M, Bertoni AG, Schreiner PJ, Roux AV, et al. Examining a bidirectional association between depressive symptoms and diabetes. *Jama* 2008;299(23):2751-9.
11. Istvan J, Zavela K, Weidner G. Body weight and psychological distress in NHANES I. *Int J Obes Relat Metab Disord* 1992;16(12):999-1003.
12. Crisp AH, McGuinness B. Jolly fat: relation between obesity and psychoneurosis in general population. *Br Med J* 1976;1(6000):7-9.
13. Magnusson PK, Rasmussen F, Lawlor DA, Tynelius P, Gunnell D. Association of body mass index with suicide mortality: a prospective cohort study of more than one million men. *Am J Epidemiol* 2006;163(1):1-8.
14. Andreyeva T, Puhl RM, Brownell KD. Changes in perceived weight discrimination among Americans, 1995-1996 through 2004-2006. *Obesity (Silver Spring)* 2008;16(5):1129-34.
15. Pallister E, Waller G. Anxiety in the eating disorders: understanding the overlap. *Clin Psychol Rev* 2008;28(3):366-86.
16. Dallman MF, Pecoraro N, Akana SF, La Fleur SE, Gomez F, Houshyar H, et al. Chronic stress and obesity: a new view of "comfort food". *Proc Natl Acad Sci U S A* 2003;100(20):11696-701.
17. Sussman N, Ginsberg DL, Bikoff J. Effects of nefazodone on body weight: a pooled analysis of selective serotonin reuptake inhibitor- and imipramine-controlled trials. *J Clin Psychiatry* 2001;62(4):256-60.
18. Compton WM, Conway KP, Stinson FS, Grant BF. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991-1992 and 2001-2002. *Am J Psychiatry* 2006;163(12):2141-7.
19. Kopelman PG. Obesity as a medical problem. *Nature* 2000;404(6778):635-43.
20. Marmot MG, Davey Smith G, Stansfeld S, Patel C, North F, Head J, et al. Health inequalities among British civil servants: the Whitehall II study. *Lancet* 1991;337(8754):1387-93.
21. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994;90(1):583-612.

22. Goldberg DP. *Detecting Psychiatric Illness by Questionnaire*. London: Oxford University Press, 1972.
23. Huppert FA, Whittington JE. Symptoms of psychological distress predict 7-year mortality. *Psychol Med* 1995;25(5):1073-86.
24. Stansfeld SA, Marmot MG. Social class and minor psychiatric disorder in British Civil Servants: a validated screening survey using the General Health Questionnaire. *Psychol Med* 1992;22(3):739-49.
25. WHO. Physical status: the use and interpretation of anthropometry: report of a WHO expert committee. *WHO Technical Report Series*. Geneva: World Health Organization, 1995.
26. Prince M, Patel V, Saxena S, Maj M, Maselko J, Phillips MR, et al. No health without mental health. *Lancet* 2007;370(9590):859-77.
27. WHO. *International Classification of Diseases - 9th revision*. Geneva: World Health Organization, 1997.
28. Mead GE, Morley W, Campbell P, Greig CA, McMurdo M, Lawlor DA. Exercise for depression. *Cochrane Database Syst Rev* 2008(4):CD004366.
29. Demyttenaere K, Jaspers L. Review: Bupropion and SSRI-induced side effects. *J Psychopharmacol* 2008;22(7):792-804.
30. Bornstein SR, Schuppenies A, Wong ML, Licinio J. Approaching the shared biology of obesity and depression: the stress axis as the locus of gene-environment interactions. *Mol Psychiatry* 2006;11(10):892-902.
31. Gluck ME, Geliebter A, Hung J, Yahav E. Cortisol, hunger, and desire to binge eat following a cold stress test in obese women with binge eating disorder. *Psychosom Med* 2004;66(6):876-81.

FIGURE LEGENDS

Figure 1. Flow chart of follow-up.

Table 1. Comparison of the characteristics of the analytic sample with those in the excluded baseline population.

Baseline characteristic	Included	Excluded*	P for heterogeneity
N	4363 (44.6)	5412 (55.4)	
Mean age†	44.0 (6.0)	44.4 (6.1)	<0.0001
Sex			
Men	3122 (71.6)	3416 (63.1)	<0.0001
Women	1241 (28.4)	1996 (36.9)	
Ethnicity			
Caucasian	4042 (92.7)	4691 (87.8)	<0.0001
Non-caucasian	319 (7.3)	651 (12.2)	
Marital status			
Married or co-habiting	3341 (76.8)	3826 (72.6)	<0.0001
Single/divorced/widow	1011 (23.2)	1442 (27.4)	
Socioeconomic position			
High	1484 (34.0)	1380 (26.1)	<0.0001
Intermediate	2256 (51.7)	2418 (45.7)	
Low	620 (14.2)	1495 (28.2)	
Smoking			
Never	2303 (53.8)	2566 (48.6)	0.005
Ex-smoker	1454 (34.0)	1671 (31.7)	
Light smoker (1-10 cigarettes per day)	198 (4.6)	310 (5.9)	
Moderate smoker (11-20 cigarettes per day)	225 (5.3)	475 (9.0)	
Heavy smoker (>20 cigarettes per day)	102 (2.4)	255 (4.8)	
Alcohol intake			
No (0 units per week)	630 (14.5)	1105 (20.6)	<0.0001
Moderate (1 - 20 units per week)	3118 (71.9)	3514 (65.6)	
Heavy (21+ units per week)	586 (13.6)	737 (13.8)	
Physical exercise			
Mild/none	1159 (26.8)	1747 (32.9)	<0.0001
Moderate	2177 (50.4)	2525 (47.5)	
Vigorous	982 (22.7)	1039 (19.6)	
Systolic blood pressure, mm Hg†	122.1 (13.9)	123.2 (15.0)	<0.0001
Diastolic blood pressure, mm Hg†	76.2 (9.7)	77.2 (10.4)	<0.0001
Total cholesterol, mm/L†	5.88 (1.11)	5.99 (1.20)	<0.0001
Diabetes			

...**Table 1 (cont)**. Comparison of the characteristics of the analytic sample with those in the excluded baseline population.

No	4318 (99.5)	5303 (98.9)	0.001
Yes	22 (0.5)	61 (1.1)	
Coronary heart disease			
No	4338 (99.4)	5351 (98.9)	<0.0001
Yes	25 (0.6)	61 (1.1)	
Use of psychotropic drug			
No	4239 (97.2)	5090 (96.2)	0.005
Yes	121 (2.8)	202 (3.8)	
GHQ caseness			
No	3199 (73.3)	3848 (72.6)	0.45
Yes	1164 (26.7)	1450 (27.4)	
BMI category			
Normal weight	2793 (64.0)	3179 (58.7)	
Overweight	1356 (31.1)	1783 (32.9)	
Obese	214 (4.9)	450 (8.3)	<0.0001
BMI (kg/m ²)†	24.3 (3.2)	24.8 (3.7)	<0.0001

Results are numbers (percents) or means (SD) unless otherwise stated.

GHQ = General Health Questionnaire (a measure of common mental disorder).

*Not including those 533 individuals who died during the follow-up from phase 1 to phase 7.

†N included 4363, N excluded 5412 for both age and BMI. Corresponding numbers are 4359 and 5402 for systolic and diastolic blood pressure and 4339 and 5366 for total cholesterol. Numbers for all other variables are provided in the table.

Table 2. Multivariate models of the association between occurrence of common mental disorder (GHQ-caseness) and subsequent BMI category (n=4154).

Number of times GHQ-case at Phases 1, 3 and 5	Number of participants	Odds ratio (95% CI) for overweight* vs normal weight at phase 7		
		Model A	Model A	Model B
0	2259	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1111	1.19 (0.99 to 1.41)	1.33 (1.00 to 1.77)	1.31 (0.98 to 1.76)
2	555	1.32 (1.05 to 1.66)	1.64 (1.13 to 2.36)	1.63 (1.12 to 2.37)
3	229	1.00 (0.71 to 1.40)	2.01 (1.21 to 3.34)	2.01 (1.19 to 3.39)
Test for trend		$P = 0.07$	$P < 0.0001$	$P < 0.0001$

*1518 (36.5%) normal weight, 1938 (46.7%) overweight and 698 (16.8%) obese.

Model A is adjusted for age, sex and BMI category at phase 1.

Model B is as Model A but additionally adjusted for ethnicity, marital status, socioeconomic position, smoking, alcohol intake, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, diabetes, CHD, and use of psychotropic drugs at phase 1.

Table 3. Multivariate models of the association between obesity and subsequent common mental disorder (GHQ-caseness; n=4154).

Number of times obese at phases 1, 3 and 5	Number of participants	Odds ratio (95% CI) for GHQ-caseness* at phase 7	
		Model A	Model B
0	3557	1.00 (reference)	1.00 (reference)
1	272	1.21 (0.89 to 1.62)	1.21 (0.89 to 1.63)
2	166	1.35 (0.93 to 1.97)	1.36 (0.93 to 1.99)
3	156	1.43 (0.98 to 2.10)	1.39 (0.94 to 2.05)
Test for trend		<i>P</i> = 0.01	<i>P</i> = 0.02

*834 (20.1%) were GHQ-cases at phase 7.

Model A is adjusted for age, sex and GHQ-caseness at phase 1.

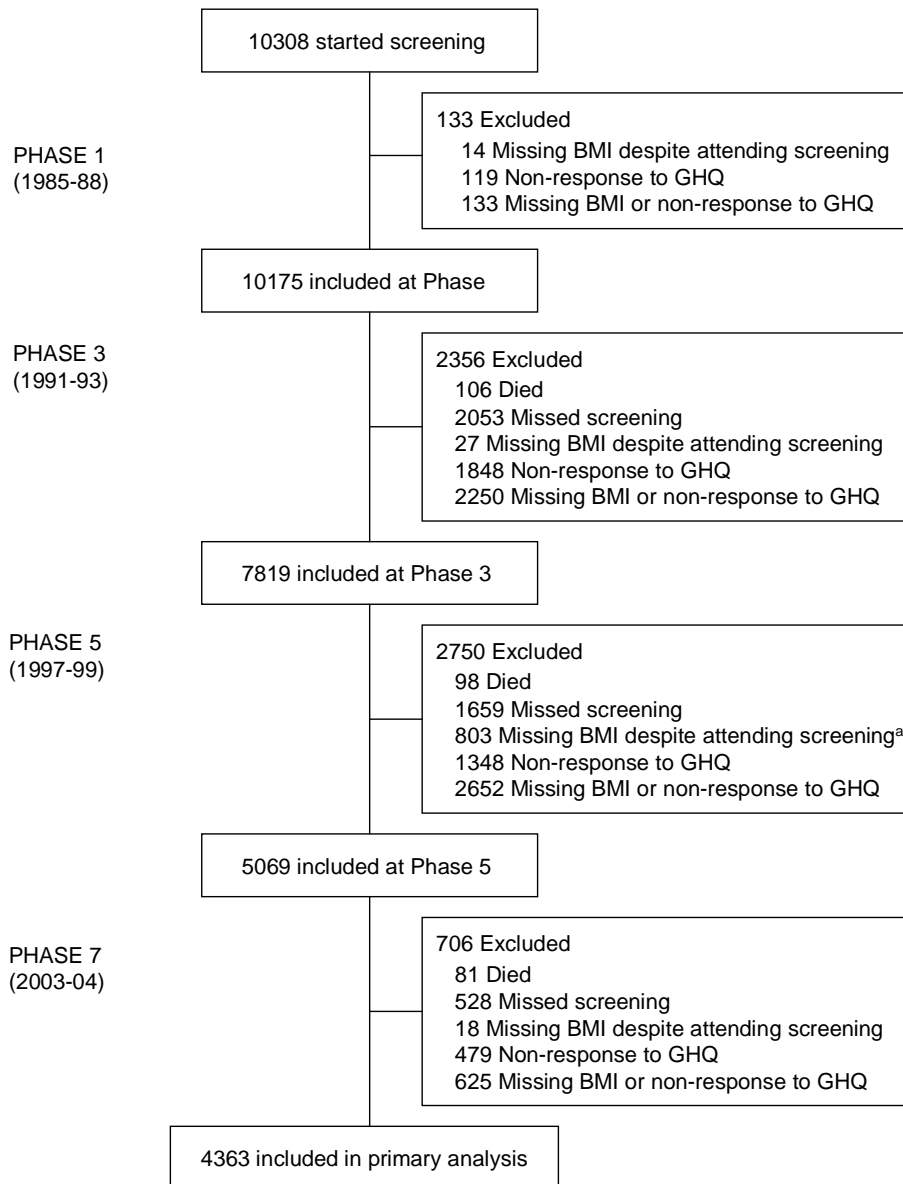
Model B is as Model A but additionally adjusted for ethnicity, marital status, socioeconomic position, smoking, alcohol intake, physical activity, systolic blood pressure, diastolic blood pressure, total cholesterol, diabetes, CHD, and use of psychotropic drugs at phase 1.

Table 4. Subgroup analyses testing temporal order between GHQ-caseness and obesity.

Subcohort at phase 1		
Exposure	Number of participants	Odds ratio (95% CI)
<u>Non-obese participants (n=4149)</u>		
Number of times ghq-case at phases 1, 3 and 5		Outcome: obese vs normal weight at phase 7*
0	2274	1.00 (reference)
1	1101	1.43 (1.03 to 1.99)
2	550	1.81 (1.19 to 2.75)
3	224	2.61 (1.45 to 4.69)
Test for trend		$P < 0.0001$
<u>Normal weight participants (n=2793)</u>		
Number of times ghq-case at phases 1, 3 and 5		Outcome: obese vs normal weight at phase 7*
0	1487	1.00 (reference)
1	762	1.39 (0.75 to 2.57)
2	338	2.05 (1.05 to 4.02)
3	156	1.89 (0.71 to 5.06)
Test for trend		$P = 0.03$
<u>Participants not GHQ-cases (n=3199)</u>		
Number of times obese at phases 1, 3 and 5		Outcome: GHQ-caseness at phase 7†
0	2746	1.00 (reference)
1	203	1.13 (0.77 to 1.66)
2	126	1.17 (0.72 to 1.88)
3	124	1.18 (0.73 to 1.90)
Test for trend		$P = 0.33$

*Adjusted for age, sex and BMI at baseline

†Adjusted for age and sex.



^a The greater number of participants with missing BMI at this phase is due to sick clinic personnel

