

# The Relationship Between Body Composition, Glucose Metabolism, and Subtypes of Depressive Symptoms – Findings From the Helsinki Birth Cohort Study

Mia D. Eriksson (✉ [mia.eriksson@helsinki.fi](mailto:mia.eriksson@helsinki.fi))

University of Helsinki

Johan G. Eriksson

Folkhälsans Forskningscentrum

Päivi Korhonen

Turku University Hospital and University of Turku

Minna K. Salonen

Finnish Institute for Health and Welfare

Tuija M. Mikkola

University of Helsinki

Eero Kajantie

Folkhälsans Forskningscentrum

Niko Wasenius

Folkhälsans Forskningscentrum

Mikaela Bonsdorff

Folkhälsans Forskningscentrum

Hannu Kautiainen

University of Eastern Finland

Merja K. Laine

University of Helsinki



---

## Research Article

**Keywords:** body composition, cohort study, comorbidity, depression, depressive disorder, depressive symptoms, fat mass index, lean mass index, obesity, overweight

**Posted Date:** September 21st, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-911998/v1>

**License:**   This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)



# Abstract

## Background

There is an existing link between two of the most common diseases, obesity and depression. These are both of great public health concern, but little is known about the relationships between the subtypes of these conditions. We hypothesized that non-melancholic depressive symptoms have a stronger relationship with both body composition (lean mass and fat mass) and dysfunctional glucose metabolism than melancholic depression.

## Methods

For this cross-sectional study 1 510 participants from the Helsinki Birth Cohort Study had their body composition evaluated as lean mass and fat mass (Lean Mass Index + Fat Mass Index = Body Mass Index). Participants were evaluated for depressive symptoms utilizing the Beck Depression Inventory, and had laboratory assessments including an oral glucose tolerance test.

## Results

Higher than average Fat Mass Index ( $\text{kg}/\text{m}^2$ ) was associated with a higher percentage of participants scoring in the depressive range of the Beck Depression Inventory ( $p=0.048$ ). Higher Fat Mass Index was associated with a higher likelihood of having depressive symptoms (OR per 1-SD Fat Mass Index=1.37, 95% CI: 1.13-1.65), whereas higher Lean Mass Index ( $\text{kg}/\text{m}^2$ ) was associated with a lower likelihood of having depressive symptoms (OR per 1-SD Lean Mass Index=0.76, 95% CI: 0.64-0.91). Participants with an above average Fat Mass Index more frequently had non-melancholic depressive symptoms ( $p=0.008$ ) regardless of Lean Mass Index levels ( $p=0.38$ ). There was no difference between the body composition groups in the likelihood of having melancholic depressive symptoms (Fat Mass Index  $p=0.83$ , Lean Mass Index  $p=0.93$ ). The non-melancholic group had higher Fat Mass Index than either of the other groups ( $p<0.001$ ), and a higher 2-hour glucose concentration than the non-depressed group ( $p=0.005$ ).

## Conclusion

As hypothesized, non-melancholic depressive symptoms are most closely related to high fat mass index and dysfunctional glucose metabolism.

## Background

Obesity and depression are both among the most common diseases globally [1], and they have been known to frequently co-occur implying a close relationship between the two. [2] Overweight, obesity and depression are of significant public health concern [1,3,4] as their prevalence continues to increase [1,3] and further contribute to the overall economic burden on society. [1,3,4]

High body mass index (BMI) both accounts for a large portion of disability-adjusted life years compared to other risk factors, and has an increasing summary exposure, which is of concern for current and future

health. [5] There were high positive rates of change for high BMI globally from 2010 to 2019. [5] In 2019 high BMI accounted for more than 6 disability-adjusted life years for each sex, and was highest among the middle and high socio-demographics. High BMI also accounted for around 5 million global attributable deaths for men and women together in 2019. [5]

By the year 2030 depression has been predicted to be the leading cause of burden of disease. [6] Currently, on a global level, depression affects more than 322 million individuals. [7] It contributes enormously to the overall burden of disease [8], and is the current worldwide leading cause of years being lost to disability. [7] Depression also comes with a two-fold increased risk of death that previous studies have not been able to explain to be a result of either behavior or physical illness. [9]

Depression is a heterogenous condition that can be divided into subtypes; melancholic and non-melancholic depression. These subtypes are known to differ in their pathophysiology. [10,11] Metabolic and inflammatory dysregulations have been implicated in the case of non-melancholic depression, with hypothalamic-pituitary-adrenal (HPA)-axis dysregulations being linked to melancholic depression. [10,11] Others suggest that the HPA-axis may be linked to both, where overactivity is related to melancholic depression and underactivity is related to non-melancholic depression. [2]

The existence of a relationship between body composition and depressive symptoms has been well established. [2–4,11–18] One hypothesis is that a relationship between obesity and depression may exist due to central and peripheral inflammation. [2] Relationships between depressive symptoms and higher fat mass, or lower muscle mass have been reported. [12] By focusing on depressive subtypes and studying how they differ in regard to body composition we may be able to learn more about the heterogeneity of depression.

There is an established relationship between depression and diabetes mellitus [19,20] although this association may not extend to people with impaired glucose metabolism or undiagnosed diabetes. [21] Some studies suggest that the association with impaired glucose metabolism is stronger in depressed individuals with anhedonia than in those without. [22] There is also some indication that specifically non-melancholic depression is associated with dysfunctional glucose metabolism. [11,23] Impaired glucose metabolism is also well known to be associated with obesity, metabolic syndrome, and body composition. [24,25]

Previous studies have primarily focused on either the subtypes of depression or individual components of body composition, without taking both into consideration simultaneously. Existing research has shown that there is a difference in body composition and glucose metabolism between those with melancholic and non-melancholic depression. [11]

The aim of this study is to evaluate the relationships between body composition, expressed as lean mass and fat mass, and subtypes of depressive symptoms. Furthermore, we want to evaluate how glucose metabolism varies with non-melancholic and melancholic depressive symptoms. We hypothesize that non-melancholic depressive symptoms have a stronger relationship with both body composition and dysfunctional glucose metabolism than melancholic depressive symptoms.

# Materials And Methods

## Participants

Helsinki Birth Cohort Study is composed of men and women born at either Helsinki University Hospital or Helsinki City Maternity Hospital in Helsinki, Finland between 1934 and 1944. The cohort consists of a total of 13 345 participants that attended child welfare clinics in Helsinki, with most participants also having attended school in Helsinki. More detailed information regarding birth, child welfare, and school records have been published elsewhere. [26,27] After receiving unique identification numbers by the Finnish government in 1971, 8 760 individuals (4 630 men and 4 130 women) from this cohort, born at Helsinki University Hospital, were identified. In 2001-2004, 2 902 subjects were selected for further studies using random-number tables. These participants were selected from the pool of the original cohort that were alive and still living in Finland. Of the subjects that were identified and selected, 2 003 individuals participated in the study. After exclusion of missing data, diabetes mellitus and high-sensitivity C-reactive protein (hsCRP )>10 mg/l [28], the final number of participants was 1 510.

## Depressive Symptoms

To assess depressive symptoms in the participants, the Beck Depression Inventory (BDI) was used. The BDI is a self-reported questionnaire consisting of 21 questions specific to depression. [29] The questionnaire is scored on a 0-63 point scale that has been validated to screen for mild to severe clinical depression with a  $\geq 10$  point cut-off. [30]

Those participants scoring  $\geq 10$  were classified as having either non-melancholic or melancholic depressive symptoms based on the presence or absence of melancholic symptoms according to the DSM-IV. We used the symptoms of sadness, past failure, loss of pleasure, guilty feelings, punishment feelings, loss of interest, irritability, changes in sleep and appetite to assess melancholy in accordance with prior publications. [23,31,32] Participants were classified as either having non-melancholic or melancholic depressive symptoms based on which summary score for the symptoms was greater. [23,31,32]

## Anthropometry and Body Composition

Height and weight were obtained using a Kawi stadiometer and a Seca Alpha 770 scale, respectively. Measurements were obtained with participants wearing light indoor clothing, and no shoes. The height and weight were measured to the nearest 0.1 cm and 0.1 kg, respectively. BMI ( $\text{kg}/\text{m}^2$ ) was calculated as weight (kg), divided by height squared ( $\text{m}^2$ ). Each participant had their body composition assessed by an eight-polar tactile electrode bio-impedance system (InBody 3.0, Biospace Co, Ltd, Seoul, Korea). Fat mass index (FMI,  $\text{kg}/\text{m}^2$ ) was calculated as measured fat mass (kg), divided by height squared ( $\text{m}^2$ ). Lean mass index (LMI,  $\text{kg}/\text{m}^2$ ) was calculated as weight minus fat mass (kg), divided by height squared ( $\text{m}^2$ ).  $\text{FMI} + \text{LMI} = \text{BMI}$ . FMI and LMI had their z-scores stratified by sex and then combined once standardized, creating four distinct categories for body composition; A) above mean FMI and below mean LMI, B) above mean FMI and above mean LMI, C) below mean FMI and below mean LMI, D) below mean FMI and above mean LMI. [33]

## Other Measurements

Participants had blood drawn after an overnight fast for laboratory assessment. These included hsCRP, glucose, insulin, and lipids. hsCRP was measured using a photometric immunochemical method. Plasma glucose was measured by a hexokinase method at 0 minutes (fasting), 30 minutes and 120 minutes after a 75 g oral glucose tolerance test (OGTT). Fasting plasma insulin was measured by two-site immunometric assay. (34) Total cholesterol and lipids were measured by standard enzymatic methods. [35,36] Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated as  $[(\text{fasting plasma glucose in mmol/l} \times \text{fasting plasma insulin in mU/l}) / 22.5]$ . [37,38]

Blood pressure was measured with the subject in a seated position. Two measurements were obtained from the right arm with a standard sphygmomanometer. The reported values are the means of the two readings. Pulse pressure was calculated as the difference between the mean systolic pressure and mean diastolic pressure.

Physical activity was assessed using the validated 12-month leisure-time physical activity (LTPA) questionnaire from the Kuopio Ischaemic Heart Disease Risk Factor Study. [39] Participants reported their activity over the past 12 months as typical intensity, frequency (occasions per month), and average duration. Utilizing available databases, values for the metabolic equivalent of task (MET; 1 MET = 3.5 ml O<sub>2</sub> /kg/min) were assigned to each activity. [40] Total LTPA in MET-hours per week were calculated by multiplying MET by average duration and frequency divided by the weeks.

Information regarding alcohol consumption and smoking, in addition to socioeconomic factors (years of education, and cohabitation) and health status were obtained through questionnaires.

## Ethics

The Coordinating Ethical Committee of the Hospital District of Helsinki and Uusimaa has approved the study protocol (344/E3/2000), and all study procedures followed the ethical guidelines of the declaration of Helsinki. Written informed consent was obtained from each subject prior to their participation.

## Statistical Analysis

The descriptive statistics were presented as means with SDs or as counts with percentages. Statistical comparisons between groups were done using analysis of variance (ANOVA), and a chi-square test. Results were also analyzed using factorial (two between-subjects factors: FMI and LMI) ANOVA and logistic models. Models included main effects of FMI and LMI and their interaction. When adjusted models were used, analysis of covariance was applied (age, sex, education, and fasting plasma glucose concentration as covariates). Hommel's adjustment was applied where appropriate to correct levels of significance for multiple testing (post hoc). Hommel's adjustment was used because it is more powerful than alternative procedures, including the Bonferroni, Holm's and Hochberg's procedures. [41] Relationship between BDI ( $\geq 10$ ) and body composition was modeled using adjusted logistic models. The bootstrap method was used when the theoretical distribution of the test statistics was unknown, or in the case of violation of the assumptions (e.g. non-normality). Correlation coefficients with 95% CI were calculated by using the Pearson

method. The normality of variables was evaluated graphically and by using the Shapiro–Wilk W test. Stata 17 (StataCorp LP; College Station, Texas, USA) statistical package was used for the analysis.

## Results

Figure 1 shows the sex-specific standardized distribution of all participants in relation to FMI and LMI. The correlation coefficient between FMI and LMI was 0.62 (95% CI: 0.59-0.65). Groups A (high FMI and low LMI), B (high FMI and high LMI), C (low FMI and low LMI), and D (low FMI and high LMI) included 197, 470, 580, and 263 cohort members, respectively.

Table 1 shows the cohort characteristics according to body composition groups. An interaction between FMI and LMI was found for sex ( $p < 0.001$ ). The proportion of women was higher in groups B and C (high FMI – high LMI, and low FMI – low LMI) than in groups D and A (low LMI – high FMI, and high LMI – low FMI). Those with high FMI had higher blood pressure, heart rate, triglyceride concentration, hsCRP, and BDI score, but lower HDL-cholesterol concentration. Those with high LMI also had higher blood pressure and triglyceride concentration, along with lower HDL-cholesterol concentration and heart rate. However, no differences in hsCRP and BDI were observed. There was an effect for high FMI on glucose concentrations at 0, 30, and 120 min after an OGTT, along with fasting insulin concentration and HOMA-IR. High LMI was related to higher fasting glucose, fasting insulin, and HOMA-IR, but there was no relation to post-load glucose concentrations.

Table 2 shows the characteristics of the participants according to which depressive subgroup they were classified into. The non-melancholic group had proportionally more women, and higher FMI than either of the other groups. Compared to the non-depressed group they also had lower LMI, higher 2-hr glucose concentration, and higher hsCRP. The melancholic group had lower total cholesterol, LDL-cholesterol, and blood pressure than either of the other two groups.

Figure 2 shows the percentage of participants in each of the four groups (A, B, C, D) that scored  $\geq 10$  on the BDI. An above average FMI was associated with a higher percentage of participants scoring in the depressive range ( $p = 0.048$ ). No effect was seen by LMI ( $p = 0.49$ ). No interaction was found ( $p = 0.26$ ). The analyses were adjusted for age, sex, education, and fasting plasma glucose concentration.

Figure 3 shows the probability of scoring  $\geq 10$  on the BDI as a continuous function of standardized FMI and LMI adjusted for age, sex, education, and fasting plasma glucose concentration. Higher FMI was associated with a higher likelihood of having depressive symptoms (OR per 1 SD FMI = 1.37 95% CI: 1.13-1.65). Higher LMI was associated with lower likelihood of having depressive symptoms (OR per 1 SD LMI = 0.76 95% CI: 0.64-0.91).

Figure 4 has been adjusted for age, sex, education, and fasting plasma glucose concentration. Participants with a high FMI more often had non-melancholic depressive symptoms ( $p = 0.008$ ) regardless of LMI levels ( $p = 0.38$ ). No interaction was found ( $p = 0.31$ ). No differences were found in the frequency of having melancholic depressive symptoms between the body composition groups (FMI  $p = 0.83$ , LMI  $p = 0.93$ ). No interaction was found ( $p = 0.52$ ).

## Discussion

As one of the two subcomponents of BMI, FMI showed a distinct relationship with a higher frequency of participants scoring in the depressive range on the BDI. When analyzing the subtypes of depressive symptoms separately no such relationship was found in the melancholic group. In accordance with our hypothesis, we found that the group with non-melancholic depressive symptoms showed a more pronounced relationship with body composition than those with melancholic depressive symptoms. More specifically, non-melancholic depressive symptoms were associated with higher FMI. This may suggest that the combined effect showing a relationship between high FMI and depressive symptoms was explained by the findings in the non-melancholic group. This is an important finding, as prior research has established the relationship between increased fat mass and depression. [12] Our findings suggest that this may be limited to non-melancholic depressive symptoms rather than overall depressive symptoms or melancholic depressive symptoms.

Furthermore, our findings suggest that body fat mass and lean mass have opposite relationships with the prevalence of depressive symptoms. The presence of a high FMI increased the likelihood of depressive symptoms, whereas the presence of a high LMI decreased the likelihood of depressive symptoms. Since neither of these variables can exist independently of each other it is important to remember that their opposite effects will moderate each other. This further emphasizes the importance of considering these factors both individually and simultaneously.

A variety of possible explanations for the body composition – depression relationship exists. Research suggests that there may be some genetic overlap between obesity and depressive symptoms, that could be driving both states. [18] Further it has been suggested that the psychological aspects of beauty standards may play a partial role in mediating the relationship between overweight and depressive symptomatology. [1] However, a study with a 12-month follow-up found that increases in fat mass or BMI were not related to any increase in depression. [42]

The most common of the explanations for the body composition – depression relationship is that of an underlying inflammatory effect. Various inflammatory markers, including CRP, have been used as measurements of inflammatory responses within the body [1], and hsCRP was used in the current study as well. The current study found that high FMI was associated with a higher hsCRP concentration. Considering the association found between FMI and non-melancholic symptoms, it is not surprising that we found higher hsCRP concentration in the non-melancholic group than in the non-depressed group. This is in line with prior research showing that non-melancholic depressive symptoms correlate with CRP levels [11], and that those having both obesity and metabolic syndrome have the highest levels. [2]

The pathologies of both obesity and depression have inflammatory components [1,14], with obesity exhibiting chronic low-grade inflammation. [1] Visceral adipose tissue has a particularly high production of pro-inflammatory cytokines that play a role in both obesity and depression. [13] This link between the two pathologies via immunological and inflammatory pathways has been suggested to be bidirectional and self-perpetuating, leading to a vicious cycle of the body composition – depression relationship being exaggerated over time. [1] Research has also been able to show that brain-derived neurotrophic factor, which



is associated with obesity in humans, can be downregulated as a result of inflammation driven emotional changes in animals. [1] This provides a possible explanation of how the inflammatory pathway may work, but overall little is still known about the details of the inflammatory connection.

We did not detect any difference in hsCRP concentrations between the melancholic and non-melancholic groups. This may simply be due to the low power of the melancholic group. Melancholic depression has been shown to have lower inflammatory markers than non-melancholic depression [11], and may hence not be part of this obesity – depression relationship. The current thinking is that melancholic depression is not associated with inflammation, but rather with a change in the HPA-axis regulation. [11] If the thought that inflammation is what causes the changes in body composition is true, then this would explain why there is no association between melancholic depression and higher FMI. To accurately assess changes in the HPA-axis, multiple parameters need to be tested [2], making any such analysis extremely difficult. It has however been reported that cortisol levels are positively associated with melancholic depression. [11] Further, research involving Cushing's syndrome has been able to show a causal relationship between cortisol and depression. [1]

It is of importance to note that some participants in the present study had comorbid diseases that could possibly have influenced our findings. Of note are especially cardiovascular disease, which was more prevalent in the high FMI group. Our findings indicate that group B (high fat mass and high lean mass) had the highest prevalence of cardiovascular disease, which is in agreement with previous research indicating that the combination of high FMI and high LMI is in fact predictive of development of diabetes. [43] This same body composition profile was also associated with the highest cardiometabolic risk. [43]

Both lower LMI and lower FMI show a relationship with lower fasting plasma glucose levels. However, glucose metabolism seems to be more related to FMI as indicated by higher glucose concentrations at 30 and 120 minutes after an OGTT. It has previously been shown that non-melancholic depression is more closely related to higher fasting glucose concentrations than melancholic depression is. [11,23] Here, however, we found no differences between the depressive subtypes for fasting glucose, but at 2 h after the OGTT the non-melancholic group showed higher glucose concentrations than the non-depressed group. Plasma glucose 2h after an OGTT has been shown to be a better predictor of mortality than fasting glucose. [44] Furthermore, impaired glucose metabolism is known to be a cardiovascular risk factor. [44,45] Since all diabetics were excluded from our study sample the glucose concentrations are within the normal range even though there is a difference between the groups. The values themselves do not infer a greater risk of cardiovascular disease than the general population, but the difference between the group can serve as an indication of some underlying difference in glucose regulation in the non-melancholic group. This is in line with the findings that non-melancholic depression is associated with body composition, as glucose metabolism is often altered in obesity, and both are associated with depression. [1]

In accordance with prior research [33] we showed that blood pressure has a main effect, with both higher LMI and FMI being related to higher blood pressure. This is true for both systolic and diastolic pressures. For the depressive subtypes we were able to show that the melancholic group has both lower systolic and diastolic blood pressure than either the non-depressed or the non-melancholic group. Higher blood pressure

has been associated with both obesity and elevated glucose concentrations in depressed individuals. [10] Melancholic depressed individuals have previously been shown to have lower systolic blood pressure than non-depressed individuals. [11] This is all in line with our findings of the non-melancholic group having a stronger relationship with dysfunctional glucose metabolism and body composition.

Previous studies have reported sex-differences in the body composition – depression relationship [14], with women displaying a stronger relationship than men. [1,16,17] However, it has been suggested that the difference may be due to the sex-specific body compositions. [13] Ideally all factors could have been analyzed separately for both sexes, which would have allowed us to evaluate for differences between men and women. While we were not able to stratify the analyses according to gender due to limited power in the analyses, we standardized the body compositions factors by sex around their sex-specific means in order to effectively eliminate the sex-specific differences in body composition due to the differences in fat and lean mass distributions in men and women.

The current study has both strengths and limitations. Among the strengths are the extensively phenotyped participants, overall large sample size, and random selection of participants from the pool. The cross-sectional nature of the study is a limitation because it allows for no inferences regarding directionality or time-dependent causality. Other limitations are the presence of comorbidities among participants, and self-reported depressive symptoms rather than clinically diagnosed depressive disorders. The limited subgroup size prevented us from analyzing men and women separately, which would have been of benefit in gaining the most information possible. Ideally, we would also have had cortisol measurements for all the participants, but that information was not available. The age range could be viewed as a limitation in how these findings can be generalized to the general population, or as a strength since this minimizes the effect of aging on the results.

It would be of interest for further studies to build on these findings by introducing time as a factor. Some previous research has suggested that the body composition – depression relationship could be reinforced over time. [14] Depression has also been shown to have a relationship with long term body composition in some adolescents. [15] Another study showed that during a 12-month follow up increased BMI, visceral adiposity, or body fat did not correlate with increased depression. [42] Focusing on these same factors as the current study but in relation to lifetime body composition could be interesting. As we know birthweight and changes in weight over a lifetime can affect comorbidities differently. [26,27,46] It may be of value to know if rather than just body composition at a certain time, changes in body composition over the life course are associated with prevalence of one or the other type of depressive symptoms.

Depression is a treatable disease for which there are many effective treatment options. [47] One challenge is the heterogenous nature of depression, and the fact that currently the subtypes are only distinguished based on self-reported criteria rather than established biomarkers. [47] While depression has been increasing in prevalence, up to half of depressed individuals may be inadequately treated [47], which tells us about the need for a better understanding of this disease. Underlying pathophysiology of the depressive subtypes may be a factor in how depression could be treated more efficiently.

The novelty of the current study is that it provides more specific information differentiating between non-melancholic depressive symptoms and melancholic depressive symptoms and their relationships with FMI and LMI than previously available publications.

## Conclusion

Non-melancholic depressive symptoms are associated with high fat mass and dysfunctional glucose metabolism.

## Declarations

### Acknowledgements

Mia D. Eriksson, ORCID 0000-0001-8968-8304; Johan G. Eriksson, ORCID 0000-0002-2516-2060; Hannu Kautiainen, ORCID 0000-0003-0786-0858; Tuija M. Mikkola, ORCID 0000-0003-0885-2788; Päivi Korhonen 0000-0002-0244-4890; Merja K. Laine, ORCID 0000-0002-1848-1514

**Disclosure:** The authors report no conflict of interest.

**Funding:** The HBCS has been supported by grants from Finska Läkaresällskapet, the Finnish Special Governmental Subsidy for Health Sciences, Academy of Finland (126775, 127437, 129255, 129306, 129907, 130326, 134791, 209072, 210595, 213225, 263924, 275074 and 315690), Samfundet Folkhälsan, Liv och Hälsa, EU FP7 [Developmental Origins of Healthy Aging (DORIAN)] project number 278603, and EU H2020-PHC-2014-DynaHealth grant 633595 and EU Horizon 2020 Award 733206 LIFECYCLE (all for the Helsinki Birth Cohort Study), European Commission, Horizon2020 award 733280 RECAP), Foundation for Cardiovascular Research, Foundation for Diabetes Research, Foundation for Pediatric Research, Novo Nordisk Foundation, Signe and Ane Gyllenberg Foundation.

**Data availability:** The data is available from the corresponding author upon reasonable request.

## References

1. Milano W, Ambrosio P, Carizzzone F, De Biasio V, Di Munzio W, Foia MG, et al. Depression and Obesity: Analysis of Common Biomarkers. *Dis Basel Switz.* **8**(2) (2020).
2. Gawlik-Kotelnicka O, Strzelecki D. Adiposity in Depression or Depression in Adiposity? The Role of Immune-Inflammatory-Microbial Overlap. *Life.* **11**(2):117 (2021).
3. Capuron L, Lasselin J, Castanon N. Role of Adiposity-Driven Inflammation in Depressive Morbidity. *Neuropsychopharmacology.* **42**(1):115–28 (2017).
4. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health.* **9**(1):88 (2009).
5. Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of

- Disease Study 2019. *The Lancet*. **396**(10258):1223–49 (2020).
6. Malhi GS, Mann JJ. Depression. *Lancet Lond Engl*. **392**(10161):2299–312 (2018).
  7. WHO. Depression and Other Common Mental Disorders [Internet]. World Health Organization; 2017 January 3 [cited 2020 August 16]. Available from: <https://www.who.int/publications/i/item/depression-global-health-estimates>
  8. WHO. Depression [Internet]. World Health Organization; 2020 January 30 [cited 2020 July 25]. Available from: <https://www.who.int/news-room/fact-sheets/detail/depression>
  9. Markkula N, Suvisaari J. Prevalence, risk factors and prognosis of depressive disorders. *Duodecim Laaketieteellinen Aikakauskirja*. **133**(3):275–82 (2017).
  10. Penninx BWJH, Milaneschi Y, Lamers F, Vogelzangs N. Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile. *BMC Med*. **11**:129 (2013).
  11. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman ATF, Penninx BWJH. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry*. **18**(6):692–9 (2013).
  12. von Zimmermann C, Winkelmann M, Richter-Schmidinger T, Mühle C, Kornhuber J, Lenz B. Physical Activity and Body Composition Are Associated With Severity and Risk of Depression, and Serum Lipids. *Front Psychiatry*. **11**:494 (2020).
  13. Wiltink J, Michal M, Wild PS, Zwiener I, Blettner M, Münzel T, et al. Associations between depression and different measures of obesity (BMI, WC, WHtR, WHR). *BMC Psychiatry*. **13**:223 (2013).
  14. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. **67**(3):220–9 (2010).
  15. Zhu K, Allen K, Mountain J, Lye S, Pennell C, Walsh JP. Depressive symptoms, body composition and bone mass in young adults: a prospective cohort study. *Int J Obes*. **41**(4):576–81 (2017).
  16. Wild B, Herzog W, Lechner S, Niehoff D, Brenner H, Müller H, et al. Gender specific temporal and cross-sectional associations between BMI-class and symptoms of depression in the elderly. *J Psychosom Res*. **72**(5):376–82 (2012).
  17. Li L, Gower BA, Shelton RC, Wu X. Gender-Specific Relationship between Obesity and Major Depression. *Front Endocrinol*. **8**:292 (2017).
  18. Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, et al. Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations. *JAMA Psychiatry*. **74**(12):1214–25 (2017).
  19. Campayo A, Gómez-Biel CH, Lobo A. Diabetes and Depression. *Curr Psychiatry Rep*. **13**(1):26–30 (2011).
  20. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *J Affect Disord*. **142** Suppl:S8-21 (2012).

21. Nouwen A, Nefs G, Caramlau I, Connock M, Winkley K, Lloyd CE, et al. Prevalence of depression in individuals with impaired glucose metabolism or undiagnosed diabetes: a systematic review and meta-analysis of the European Depression in Diabetes (EDID) Research Consortium. *Diabetes Care*. **34**(3):752–62 (2011).
22. Moreira FP, Jansen K, Cardoso T de A, Mondin TC, Vieira IS, Magalhães PV da S, et al. Metabolic syndrome, depression and anhedonia among young adults. *Psychiatry Res*. **271**:306–10 (2019).
23. Seppälä J, Vanhala M, Kautiainen H, Eriksson J, Kampman O, Mäntyselkä P, et al. Prevalence of metabolic syndrome in subjects with melancholic and non-melancholic depressive symptoms. A Finnish population-based study. *J Affect Disord*. **136**(3):543–9 (2012).
24. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev*. **20**(2):157–72 (1998).
25. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. 1988. *Nutr Burbank Los Angel Cty Calif*. **13**(1):65; discussion 64, 66 (1997).
26. Barker DJP, Osmond C, Forsén TJ, Kajantie E, Eriksson JG. Trajectories of Growth among Children Who Have Coronary Events as Adults. *N Engl J Med*. **353**(17):1802–9 (2005).
27. Eriksson JG. Developmental Origins of Health and Disease – from a small body size at birth to epigenetics. *Ann Med*. **48**(6):456–67 (2016).
28. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. **107**(3):499–511 (2003).
29. Beck AT. An Inventory for Measuring Depression. *Arch Gen Psychiatry*. **4**(6):561 (1961).
30. Beck AT, Steer RA, Carbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clin Psychol Rev*. **8**(1):77–100 (1988).
31. Seppälä J, Koponen H, Kautiainen H, Eriksson JG, Kampman O, Männistö S, et al. Association between folate intake and melancholic depressive symptoms. A Finnish population-based study. *J Affect Disord*. **138**(3):473–8 (2012).
32. Vanhala M, Jokelainen J, Keinänen-Kiukaanniemi S, Kumpusalo E, Koponen H. Depressive symptoms predispose females to metabolic syndrome: a 7-year follow-up study. *Acta Psychiatr Scand*. **119**(2):137–42 (2009).
33. Korhonen PE, Mikkola T, Kautiainen H, Eriksson JG. Both lean and fat body mass associate with blood pressure. *Eur J Intern Med*. S0953620521001485 (2021).
34. Sobey WJ, Beer SF, Carrington CA, Clark PM, Frank BH, Gray IP, et al. Sensitive and specific two-site immunoradiometric assays for human insulin, proinsulin, 65-66 split and 32-33 split proinsulins. *Biochem J*. **260**(2):535–41 (1989).
35. Fossati P, Prencipe L. Serum triglycerides determined colorimetrically with an enzyme that produces hydrogen peroxide. *Clin Chem*. **28**(10):2077–80 (1982).
36. Lie RF, Schmitz JM, Pierre KJ, Gochman N. Cholesterol oxidase-based determination, by continuous-flow analysis, of total and free cholesterol in serum. *Clin Chem*. **22**(10):1627–30 (1976).

37. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. **28**(7):412–9 (1985).
38. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. **27**(6):1487–95 (2004).
39. Lakka TA, Salonen JT. Intra-Person Variability of Various Physical Activity Assessments in the Kuopio Ischaemic Heart Disease Risk Factor Study. *Int J Epidemiol*. **21**(3):467–72 (1992).
40. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: A Second Update of Codes and MET Values. *Med Sci Sports Exerc*. **43**(8):1575–81 (2011).
41. Wright SP. Adjusted P-Values for Simultaneous Inference. *Biometrics*. **48**(4):1005 (1992).
42. Cameron N, Godino JG, Skipper T, Dillon L, Waalen J, Hill L, et al. Associations between reliable changes in depression and changes in BMI, total body fatness and visceral adiposity during a 12-month weight loss trial. *Int J Obes*. **43**(9):1859–62 (2019).
43. Rehunen SKJ, Kautiainen H, Korhonen PE, Eriksson JG. A high lean body mass is not protecting from type 2 diabetes in the presence of a high body fat mass. *Diabetes Metab*. **47**(6):101219 (2021).
44. Glucose Tolerance and Cardiovascular Mortality: Comparison of Fasting and 2-Hour Diagnostic Criteria. *Arch Intern Med*. **161**(3):397 (2001).
45. Rapoport M, Chetrit A, Cantrell D, Novikov I, Roth J, Dankner R. Years of potential life lost in pre-diabetes and diabetes mellitus: data from a 40-year follow-up of the Israel study on Glucose intolerance, Obesity and Hypertension. *BMJ Open Diabetes Res Care*. **9**(1):e001981 (2021).
46. Bjerregaard LG, Wasenius N, Nedelec R, Gjørde LK, Ängquist L, Herzig K-H, et al. Possible Modifiers of the Association Between Change in Weight Status From Child Through Adult Ages and Later Risk of Type 2 Diabetes. *Diabetes Care*. **43**(5):1000–7 (2020).
47. Akil H, Gordon J, Hen R, Javitch J, Mayberg H, McEwen B, et al. Treatment resistant depression: A multi-scale, systems biology approach. *Neurosci Biobehav Rev*. **84**:272–88 (2018).

## Tables

**Table 1. Characteristics of participants by group.**

	High FMI		Low FMI		P-value		
	<b>A</b>	<b>B</b>	<b>C</b>	<b>D</b>	Main effect		Interaction
	Low LMI n=197	High LMI n=470	Low LMI n=580	High LMI n=263	FMI	LMI	
Women, n (%)	96(49)	281(60)	341(59)	124(47)	0.65	0.92	<0.001
Age (years), mean (SD)	61.3(3.2)	61.2(3.0)	60.9(2.9)	60.6(2.5)	0.002	0.15	0.65
Education (years), mean (SD)	11.9(3.6)	11.9(3.4)	12.7(3.8)	13.1(3.7)	<0.001	0.38	0.33
Cohabiting, n (%)	149(76)	358(76)	428(74)	207(79)	0.86	0.26	0.36
Current smoker, n (%)	42(21)	103(22)	136(23)	75(29)	0.075	0.26	0.39
Alcohol consumption, n(%)					0.023	0.005	0.12
0	18(9)	32(7)	45(8)	7(3)			
1-2/ month	76(39)	205(44)	213(37)	105(40)			
≥ 1/ week	102(52)	229(49)	321(55)	150(57)			
LTPA (METh/week), mean (SD)	37.8(29.0)	35.7(26.0)	40.1(27.3)	40.8(28.1)	0.016	0.65	0.37
BMI (kg/m <sup>2</sup> ), mean (SD)	27.4(1.4)	31.7(3.5)	23.4(1.9)	26.3(1.5)	<0.001	<0.001	<0.001
BP (mmHg), mean (SD)							
Systolic	146(20)	148(19)	139(20)	143(19)	<0.001	0.007	0.42
Diastolic	90(10)	92(10)	86(10)	88(10)	<0.001	0.002	0.60
Pulse pressure	56(17)	57(15)	53(15)	55(14)	0.016	0.16	0.49
Pulse (bpm)	70(12)	69(11)	69(11)	67(10)	0.008	0.003	0.16
Glucose (mmol/l), mean (SD)							
0 min	5.51(0.57)	5.63(0.56)	5.37(0.54)	5.48(0.53)	<0.001	<0.001	0.93

30 min	9.17(1.69)	9.27(1.52)	8.80(1.73)	8.81(1.60)	<0.001	0.57	0.62
120 min	7.22(1.67)	7.25(1.65)	6.50(1.65)	6.59(1.75)	<0.001	0.53	0.78
Fasting insulin ( $\mu$ U/ml) mean (SD)	11.1(14.8)	13.8(16.5)	7.2(4.2)	7.8(4.1)	<0.001	0.008	0.10
HOMA-IR, mean (SD)	2.74(3.51)	3.52(4.48)	1.73(1.08)	1.92(1.07)	<0.001	0.003	0.073
Total Cholesterol (mmol/l), mean (SD)	6.06(1.11)	6.04(1.07)	5.93(0.97)	6.00(1.03)	0.15	0.59	0.44
LDL- cholesterol (mmol/l), mean (SD)	3.78(0.91)	3.78(0.89)	3.61(0.82)	3.77(0.87)	0.083	0.10	0.10
HDL- cholesterol (mmol/l), mean (SD)	1.59(0.42)	1.53(0.38)	1.76(0.44)	1.63(0.42)	<0.001	<0.001	0.15
Triglycerides, (mmol/l), mean (SD)	1.51(0.71)	1.66(0.85)	1.23(0.61)	1.33(0.64)	<0.001	0.001	0.53
hsCRP (mg/l), mean (SD)	2.94(2.41)	2.79(2.30)	1.59(1.74)	1.78(1.86)	<0.001	0.85	0.15
Diseases, n (%)							
CVD	20(10)	40(9)	29(5)	7(3)	<0.001	0.10	0.37
Pulmonary	18(9)	59(13)	48(8)	24(9)	0.23	0.23	0.52
RA	2(1)	7(1)	11(2)	6(2)	0.26	0.55	0.83
BDI, mean (SD)	6.0(5.3)	6.2(5.6)	5.4(5.0)	4.9(4.5)	<0.001	0.54	0.20
BDI subtype, n (%)					0.44	0.19	0.18
<10	159(81)	367(78)	480(83)	230(87)			
NMeD	28(14)	76(16)	64(11)	19(7)			
MeD	10(5)	27(6)	36(6)	14(5)			



*Note.* BDI=Beck Depression Inventory, BMI=body mass index, BP=blood pressure, bpm=beats per minute, CVD=cardiovascular disease, FMI=fat mass index, HDL=high density lipoprotein, HOMA-IR= homeostatic model assessment for insulin resistance, hsCRP= high sensitivity C-reactive protein, LDL=low density lipoprotein, LMI=lean mass index, LTPA=leisure-time physical activity, MeD=melancholic depressive symptoms, NMeD=non-melancholic depressive symptoms, RA=rheumatoid arthritis, SD=standard deviation.

Disease subgroups: *CVD*: angina pectoris, myocardial infarction, stroke; *Pulmonary*: asthma, chronic obstructive pulmonary disease.

Glucose measurements were taken after a 75 g oral glucose tolerance test.

**Table 2. Characteristics according to depressive subtypes.**

	<b>BDI &lt;10</b>	<b>NMeD</b>	<b>MeD</b>	P-value [multiple comparison] *
	[X]	[Y]	[Z]	
	N=1236	N=187	N=87	
Women, n (%)	651(53)	143(76)	48(55)	<0.001 [X/Y, Y/Z]
Age (years), mean (SD)	61(3)	62(3)	61(3)	0.061
Education (years), mean (SD)	12.5(3.7)	11.7(3.3)	11.9(3.5)	0.005 [X/Y]
Cohabiting, n (%)	954(77)	127(68)	61(70)	0.011 [X/Y]
Current smoker, n (%)	284(23)	48(26)	24(28)	0.48
Alcohol consumption, n (%)				0.005 [X/Y, X/Z]
0	67(5)	22(12)	13(15)	
1–2/ month	489(40)	76(41)	34(39)	
≥ 1/ week	674(55)	88(47)	40(46)	
LTPA (METH/week), mean (SD)	38(27)	39(32)	41(28)	0.70
BMI (kg/m <sup>2</sup> ), mean (SD)	26.9(3.9)	28.2(5.4)	26.8(4.6)	<0.001 [X/Y, Y/Z]
FMI, crude mean (SD)	7.7(3.1)	9.6(4.1)	7.9(3.6)	<0.001 [X/Y, Y/Z]
LMI, crude mean (SD)	19.1(2.1)	18.6(2.2)	18.8(2.2)	0.006 [X/Y]
Blood pressure (mmHg), mean (SD)				
Systolic	144(20)	146(19)	137(20)	0.004 [X/Z, Y/Z]
Diastolic	89(10)	89(10)	85(9)	<0.001 [X/Z, Y/Z]
Pulse pressure	55(15)	56(15)	53(17)	0.20
Pulse (bpm)	69(11)	70(12)	69(13)	0.67
Glucose (mmol/l), mean (SD)				
0 min	5.49(0.54)	5.49(0.61)	5.50(0.62)	0.96
30 min	8.95(1.62)	9.22(1.69)	9.13(1.98)	0.10
120 min	6.78(1.70)	7.21(1.65)	6.94(1.72)	0.005 [X/Y]
Fasting insulin (μU/ml), mean (SD)	9.8(11.8)	11.2(11.3)	8.4(5.1)	0.15
HOMA-IR, (mean (SD))	2.43(3.12)	2.80(2.86)	2.10(1.34)	0.16
Total Cholesterol (mmol/l),	6.01(1.03)	6.02(1.05)	5.65(0.99)	0.005 [X/Z, Y/Z]

mean (SD)				
LDL-cholesterol (mmol/l),	3.75(0.86)	3.65(0.88)	3.38(0.79)	<0.001 [X/Z, Y/Z]
mean (SD)				
HDL-cholesterol (mmol/l),	1.64(0.42)	1.70(0.43)	1.62(0.49)	0.14
mean (SD)				
Triglycerides, (mmol/l),	1.40(0.71)	1.50(0.84)	1.45(0.78)	0.24
mean (SD)				
hsCRP (mg/l), mean (SD)	2.11(2.08)	2.49(2.25)	2.29(2.39)	0.045 [X/Y]
Diseases, n (%)				
CVD	61(5)	20(11)	15(17)	<0.001 [X/Y, X/Z]
Pulmonary	104(8)	33(18)	12(14)	<0.001 [X/Y]
RA	20(2)	4(2)	2(2)	0.66
BDI, mean (SD)	3.7(2.7)	14.4(5.2)	13.8(4.6)	

\* Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing (p<0.05)

*Note.* BDI=Beck Depression Inventory, BMI=body mass index, bpm=beats per minute, CVD=cardiovascular disease, FMI=fat mass index, HDL=high density lipoprotein, HOMA-IR= homeostatic model assessment for insulin resistance, hsCRP= high sensitivity C-reactive protein, LDL=low density lipoprotein, LMI=lean mass index, LTPA=leisure-time physical activity, MeD=melancholic depressive symptoms, NMeD=non-melancholic depressive symptoms, RA=rheumatoid arthritis, SD=standard deviation.

Disease subgroups: *CVD*: angina pectoris, myocardial infarction, stroke; *Pulmonary*: asthma, chronic obstructive pulmonary disease.

## Figures

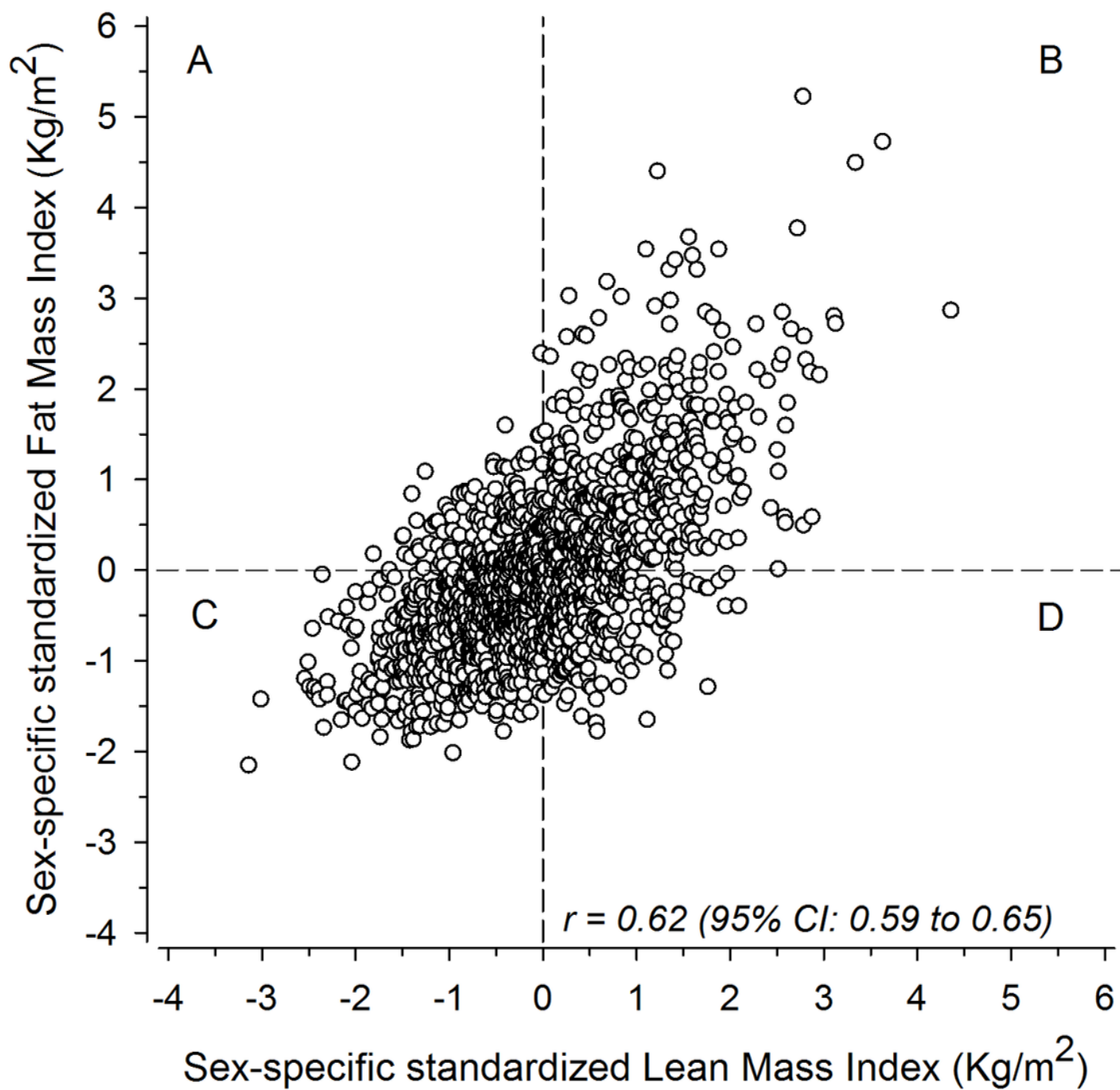
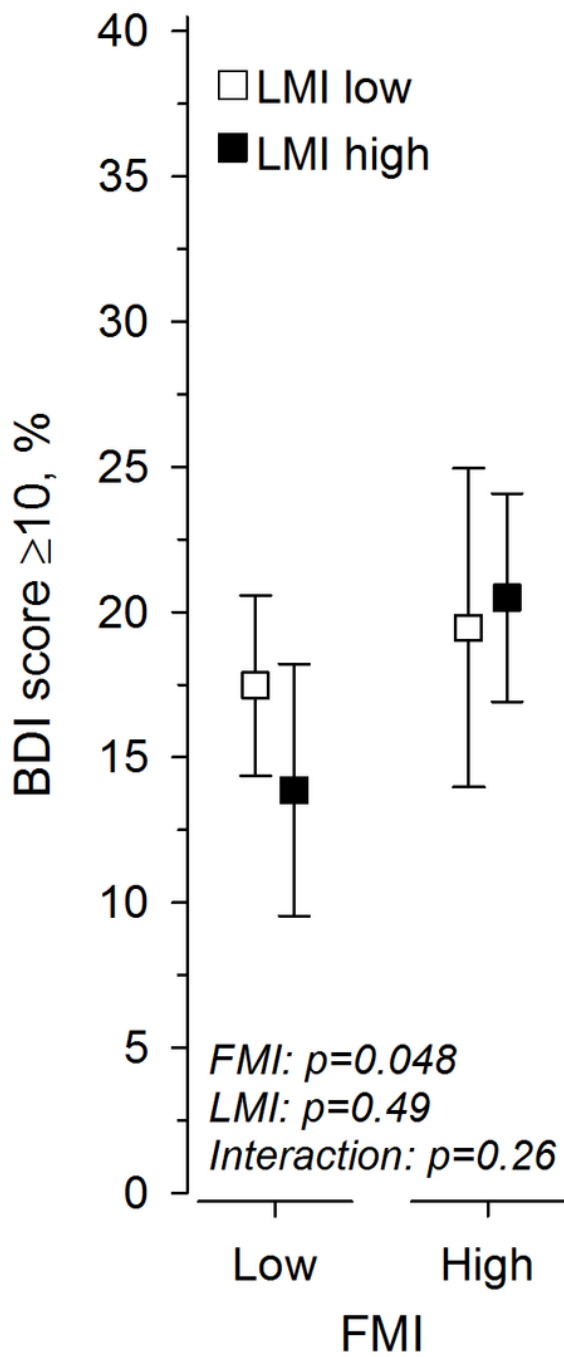


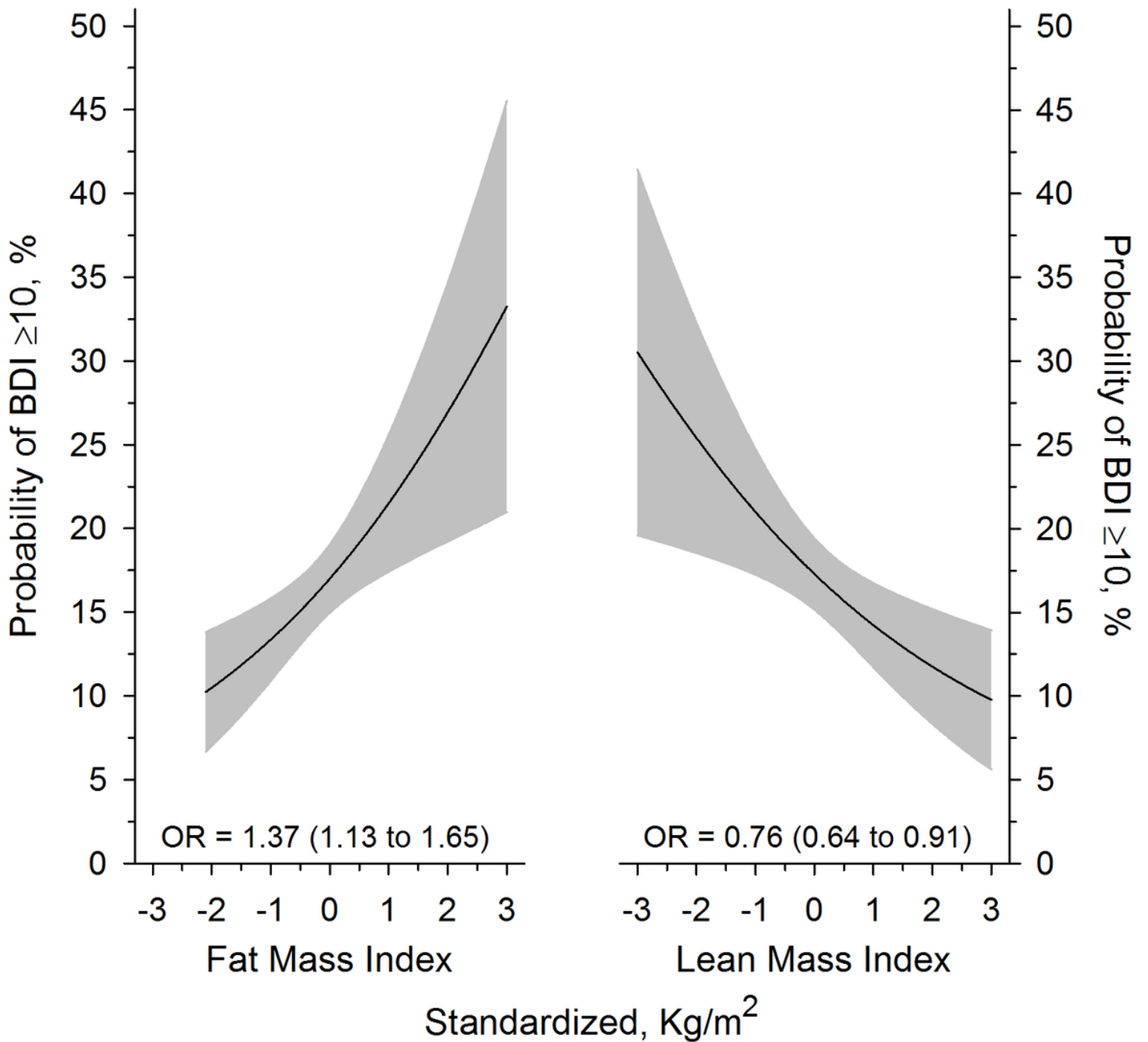
Figure 1

Categorizing participants into groups based on sex-specific standardized Fat Mass Index (FMI) and Lean Mass Index (LMI). Note. The dashed lines represent mean values. Both axes represent z-scores. The letters A, B, C, D represent the 4 body composition groups. A: above mean fat mass index (FMI) and below mean lean mass index (LMI), B: above mean FMI and above mean LMI, C: below mean FMI and below mean LMI, D: below mean FMI and above mean LMI.



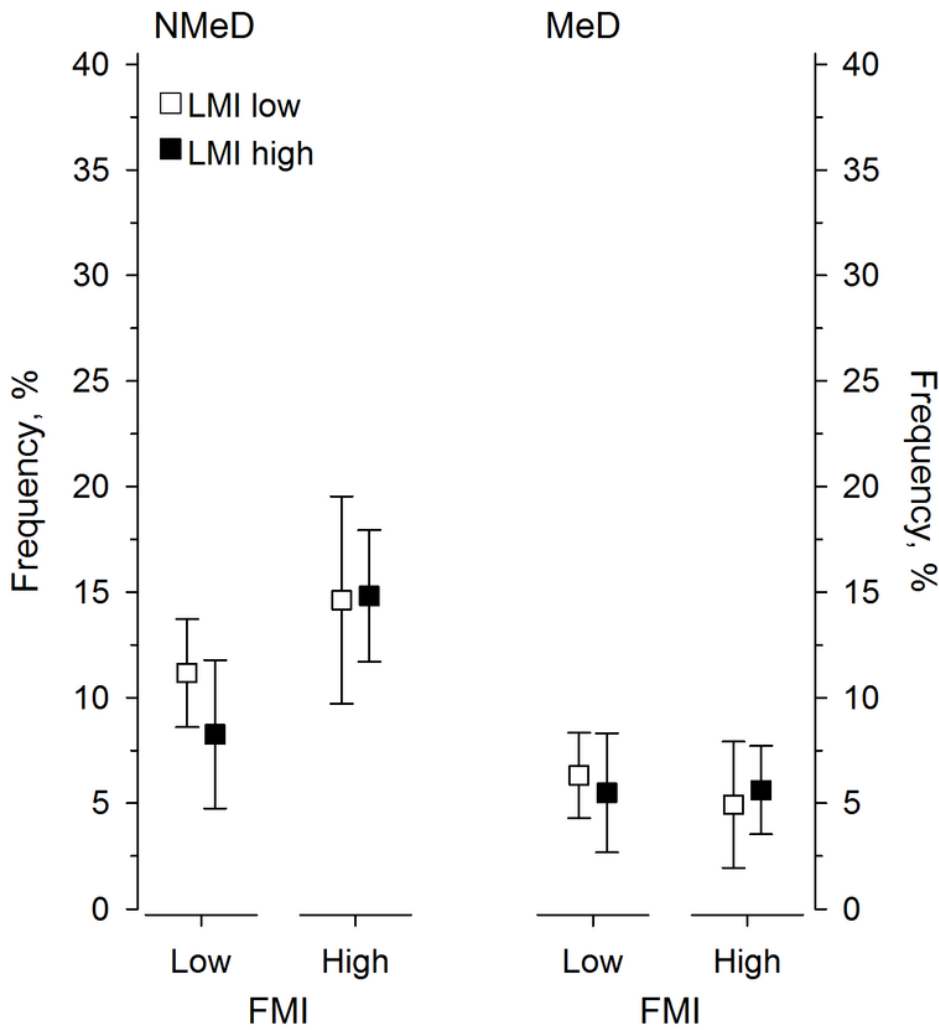
**Figure 2**

Percentage of BDI  $\geq 10$  according to body composition group Note. FMI=fat mass index, LMI=lean mass index, BDI=Beck Depression Inventory. The model has been adjusted for age, sex, education, and fasting plasma glucose concentration.



**Figure 3**

Relationship between BDI  $\geq 10$  according to body composition. Note. BDI=Beck Depression Inventory, OR= Odds Ratio. Odds ratio is presented per 1-SD. Models have been adjusted for age, sex, education, and fasting plasma glucose concentration.



**Figure 4**

Frequency of  $\geq 10$  BDI in relation to body composition group and depressive subtype as represented by mean and standard deviation Note. BDI=Beck Depression Inventory, FMI=fat mass index, LMI=lean mass index, MeD=melancholic depressive symptoms, NMeD=non-melancholic depressive symptoms. Models have been adjusted for age, sex, education, and fasting plasma glucose concentration. NMeD: FMI  $p=0.008$ , LMI  $p=0.38$ , interaction  $p=0.31$ . MeD: FMI  $p=0.83$ , LMI  $p=0.93$ , interaction  $p=0.52$ .