Disentangling the relationship between depression, obesity and cardiometabolic disease

Alshehri, T.

1

Introduction

INTRODUCTION

Obesity, depression, and cardiometabolic diseases are known as "diseases of modernity" due to the alarmingly increased prevalence since the last century [1, 2]. The first notion of the link between obesity and depression was made by Mary E. Moore in 1962 [3]. This was followed by epidemiological studies, which confirmed [4] the presence of this association. Simultaneously, epidemiological studies also reported on the link between obesity and cardiometabolic diseases [5], and depression and cardiometabolic diseases [6-9]. However, the links between these conditions appear complex and not fully understood. The comprehensive aim of this thesis is to elucidate the nature of the relationship between depression, obesity, and cardiometabolic diseases by investigating the heterogeneity of the three conditions.

Depression, obesity and cardiometabolic diseases: a complex relationship

Depression is the state of low mood and/or persistent inability to feel pleasure or reword accompanied by emotional, cognitive and somatic symptoms [10] and has been shown to be linked to obesity and cardiometabolic diseases (Table 1). The "Global burden of diseases" between 1999-2019 showed that depression, obesity and cardiometabolic diseases were among the ten leading causes of the highest absolute number of days lost for disability and premature death [11, 12]. Individuals with depression are at 58% increased risk of developing obesity [13] and 40% increased risk of premature death due to other comorbid diseases such as cardiometabolic diseases [14, 15]. To be diagnosed with depression, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, a person should report having substantial functional impairment with five out of nine symptoms for more than two weeks; two of them should be fundamental symptoms of depressed mood and anhedonia [10]. DSM contains four emotional symptoms (depressed mood, anhedonia, feeling of worthlessness or guilt, and suicidal ideation), three neurovegetative symptoms (low energy level, increased or decreased sleep, and increased or decreased weight), and finally, two neurocognitive symptoms (ability to think or concentrate or indecisiveness, and psychomotor retardation or agitation) [10, 16]. Depression can be assessed via structured clinical diagnostic interview such as the Composite International Diagnostic Interview (CIDI, version 2.1)) (then labelled as clinical depression or major depressive disorder (MDD) or a validated self-report questionnaires with specific cut-offs used to defined participants with depressed mood. Many instruments have been developed to extensively assess depressive symptomatology [17]. For example, the Inventory of Depressive Symptomatology (IDS-SR30) assesses (via a 4-points likert scale) the presence during the last week and the severity of the core symptoms of a major depressive episodes, melancholic

(e.g., anhedonia, non-reactive mood, psychomotor retardation/agitation, appetite or weight decrease, early morning awakening and self-outlook) and atypical (e.g., mood reactivity, leaden paralysis, weight gain or increased appetite, hypersomnia, and interpersonal sensitivity) features, and commonly associated symptoms (e.g., irritability, anxiety, somatic complaints) [18].

Table 1. The association between depression and cardiometabolic diseases

	Cross-sectional studies from meta-analyses	Longitudinal studies from meta-analyses	
Cardiometabolic disease	Depression-Cardiometabolic disease	Depression-> Cardiometabolic disease	Cardiometabolic disease->Depression
Obesity [1]	Pooled OR range (1.14-1.41)	Pooled OR range (from 1.37 to 1.71)	Pooled OR range (from 1.19 - to 2.15)
Type 2 diabetes [2, 3]	OR: 2.9, 95% CI 2.3–3.7	RR: 1.60 (95% CI 1.37-1.88)	RR: 1.15 (95% CI 1.02-1.30)
Cardiovascular disease:			
Ischaemic heart disease [4,5]	OR: 1.88, 95% CI, 1.59–2.23	HR: 1.63 (95% CI 1.36-1.95)	HR: 1.79 (95% CI 1.43-2.23)
stroke [6,7]	OR: 1.53, 95% CI 1.8-1.84	HR: 1.94 (95% CI 1.63-2.30)	HR: 2.62 (95% CI 2.09-3.29)

Obesity is characterized by a shift in energy balance toward excessive storing of fat droplets in adipose tissue, which is associated with low-grade inflammation and impairment of metabolic flexibility (i.e., impairment of sensing and trafficking essential substances for cellular energy homeostasis) [19]. Obesity is defined based on body mass index, which is calculated as weight (kg) divided by squared height (m^2). The World Health Organization (WHO) standard measure for defining obesity is BMI ≥ 30) [20]. Globally, the prevalence of overweight and obesity has been continuously increasing since the 1980s, and if trends do not level off or reverse, more than half of the world's adult population could be overweight or obese by 2030 [2]. Moreover, obesity is a complex condition and is also comorbid with other complex diseases such as depression, type 2 diabetes, heart disease, and stroke (Table 1) [21].

There is compelling epidemiological evidence that confirms that obesity and depression are associated [4, 13, 22, 23] in cross-sectional (Table 1; pooled odds ratios from 6 meta-analyses ranged from 1.14-1.41) and bi-directionally in longitudinal settings (Table 1; pooled odds ratios for depression as an outcome ranged from 1.19 to 2.15, and for obesity as an outcome from 1.37 to 1.71). This association between obesity and depression is only partially explained by distal factors such as lifestyle, medication, and comorbidity [4, 13, 22]. Hence the hypothesis is that there is a high potential for an underlying biological link.

Heterogeneity of depression and obesity

Depression is a heterogeneous condition [24], as the depression diagnosis, by definition, allows for many ways for the DSM criteria to be met [25, 26]. To understand depression heterogeneity, various subtypes of depression have been described [27]. Two clinical depression subtypes, the atypical depression and the melancholic depression [28, 29], have traditionally received more attention. Atypical depression is characterized by mood reactivity (i.e., mood brightens in response to positive events), fatiguability, excessive sleepiness, hyperphagia, weight gain, and interpersonal rejection sensitivity [28]. Melancholic depressive symptoms reflect a state of the hyperarousal stress response, characterized by the inability to have pleasure or reward, pronounced feelings of worthlessness, non-reactive mood, psychomotor disturbances (agitation or retardation), insomnia, loss of appetite and weight, having the worse mood early in the morning [29]. However, this concept of distinct binary depression subtypes has been criticized as it is almost impossible for the subtypes not to overlap [27]. More recently, data-driven approaches have been used in an attempt to perform cluster analysis for depressive symptoms in relation to biomarkers and clinical features. In the top-down approach, studies [30, 31] investigators performed depressive symptom-based clustering as a first step and subsequently evaluated the clustering results via association with biomarker levels. These studies reported that a cluster of atypical energy-related depressive symptoms, such as increased weight and fatigue, were associated with metabolic and inflammatory dysregulations [30, 31]. In contrast, in bottom-up approach studies [32, 33], biomarker-based clustering was done as a first step, and subsequently, the clustering results were evaluated via association with clinical features. These studies led to reports of a cluster of participants with higher metabolic and inflammatory markers who tended to be more vulnerable to depression [32, 33].

Regardless of the differences in the definitions of the different subtypes, accumulated scientific evidence highlighted that individuals who express behavioural symptoms related to energy homeostasis (as a dimension or continuous score of symptoms and not as a binary subtype) are most likely to have increased: BMI, total body fat, proinflammatory markers, acute phase proteins (i.e., IL-6, and CRP), fasting glucose, triglycerides, blood pressure, waist circumference, insulin resistance, leptin resistance and inflammation-related tryptophan catabolites (i.e., kynurenine and quinolinic acid), and decreased HDL-cholesterol [22, 34-40]. Milaneschi et al. [24] conceptualized these findings in the "immuno-metabolic depression" hypothesis, where they postulated the existence of an "immune-metabolic depression" (IMD) dimension characterized by the clustering of depressive symptoms, namely atypical energy-related symptoms (i.e., increased sleepiness, increased appetite, increased weight, low energy level and leaden paralysis) with immuno-metabolic dysregulations such as adiposity,

hyperglycaemia, dyslipidaemia, and inflammation. This model is characterized by the presence of immuno-metabolic dysregulation linked to behavioural symptoms that favour a homeostatic shift toward positive energy balance (increased intake and decreased expenditure) [24].

Obesity too is a heterogenous condition, which can be defined and characterized in different ways. As stated, body mass index (BMI) is the WHO standard measure for measuring obesity (BMI ≥ 30) [20]. Studies that investigated the association between obesity and depression mainly define obesity based on BMI [41-43]. BMI has a high correlation with the amount of fat stored in the body as adipose tissue, but it is also a proxy for high fat-free mass (i.e., muscle mass). Therefore, when BMI is used alone it can be problematic, for instance for interethnic comparison [20, 44] because it has been shown that total body fat storage and distribution varies among ethnic groups. For example, people from the Asian population have lower BMI and a higher tendency for abdominal fat accumulation than the European population. Therefore, the prevalence of type 2 diabetes and cardiovascular disease in the Asian population was reported in the BMI cut-off ≤25 [45]. The amount of total body fat can be directly measured and reported utilizing bioelectrical impedance analysis [46]. The term "adiposity" is used when referring to body fat. Even when total body fat is measured accurately, the location of fat accumulation (i.e., fat distribution) in the peripheral parts of the body or in between organs in the abdominal cavity (i.e., abdominal adiposity) particularly has an additive value for understanding the link between obesity and depression. Abdominal adiposity can be measured as waist circumference; furthermore, by exploiting magnetic resonance imaging, we can more accurately assess the amount of visceral adiposity [46]. A stronger association between depression and abdominal adiposity, as compared to overall adiposity, has been confirmed in previous studies [47, 48]. Previous work has indicated that obesity can affect health and disease differently [49, 50] by showing different and sometimes opposing relationship with metabolic dysregulations. [51-53]. These opposing forms of obesity have also been described as a) metabolically unhealthy obesity, which is associated with excess body fat with the presence of inflammation and metabolic dysregulation, and b) metabolically healthy obesity with excess body fat and healthy metabolic profile (favourable metabolic profile) [49, 50].

The comorbidity of obesity and depression with cardiometabolic diseases

Besides obesity and depression, this thesis will also examine how "cardiometabolic diseases" fits into this relationship. Twenty years ago, Linda Pescatello introduced the name "cardiometabolic diseases" to include all metabolic dysregulation resulting from insulin resistance (i.e., metabolic syndrome and cardiovascular disease, stroke and type 2 diabetes) [54]. Currently, the term cardiometabolic

diseases has no clear definition. Instead, it is used to describe type 2 diabetes and cardiovascular disease and their risk factors, such as insulin resistance, hypertension, hyperglycaemia, and dyslipidaemia, without clear criteria. This implies a heterogeneous nature of cardiometabolic diseases, especially with the notion that factors that predict diabetes, such as components of metabolic syndrome (high waist circumference, triglyceride, and fasting glucose, hypertension, and low HDL cholesterol), do not (or weakly) predict cardiovascular disease [55]. Following the literature in this field, we define cardiometabolic diseases as all insulin resistance related dysregulation unless we specify a subgroup of this constellation. Large meta-analyses of longitudinal studies [56-58] indicate that depression is associated with an increased risk of cardiometabolic diseases (i.e., myocardial infarction, type 2 diabetes, and stroke). Moreover, there is evidence that diabetes, heart disease, and stroke also increase the risk of depression) [56, 58, 59]. However, the link between depression and cardiometabolic diseases is not fully understood.

Using -omics to disentangle the relationship between obesity and depression

An overlap between obesity and depression has been reported on metabolomic and genetic levels, which may indicate a shared biological mechanism between the two conditions [22, 60]. The advancement in the targeted proton nuclear magnetic resonance platform (^{1}H-NMR) spectroscopy and mass spectrometry-based (GC-MS) technologies is opening new opportunities to study obesity and depression based on their metabolic (phenotypic) signature. Metabolomics; is defined as "the study of the unique chemical fingerprints that specific cellular processes leave behind" [61]. The role of metabolic dysregulation was previously investigated in patients with depression and an animal model of depression in a few studies [62-64]. Shao et al. [63] used gas chromatography-mass spectrometry (GC-MS) to study cerebellar metabolomics in a chronic mild stress rodent model of depression. This study showed evidence that the depression model in the rodent is associated with metabolic dysregulation in glucose, lipid, and energy biosynthesis pathways. Similarly, Zheng et al. [62] found that glucose and lipid dysregulation such as polyunsaturated fatty acids, very low density lipoprotein and low density lipoprotein signalling could be potential predictors for depression. In a small sample size study (N=30), Paige et al. [64] used GC-MS to study the metabolic signature in over 60 years old patients with depression and healthy controls. They found a metabolic signature of declined gamma-aminobutyric acid (GABA), glycerol, and short-chain fatty acids such as palmitate and oleate to be linked to depression. Despite the existence of small scales of metabolomics analysis in depression, the heterogeneity of different metabolomics technologies and the heterogeneity of the depression phenotype make it hard to draw a valid conclusion about depression metabolic signature [65].

One important genetic study explored the role of metabolic dysregulation in the relationship between adiposity and depression using a Mendelian Randomization (MR) analysis [66]. Mendelian Randomization uses genetic variants for modifiable risk factors as an unconfounded instrument variable (e.g., genetic variants for obesity), leveraging the random assortment of genes from parents to offspring during gamete formation and conception [67]. Two genetic risk scores, which reflects an individual's genetic liability for a given phenotype, were created [66]. A genetic risk score is calculated as sum of number of risk alleles across all single nucleotide polymorphisms (SNPs) related to a certain trait, weighted for the SNPs' estimates derived from an independent GWAS [68]. The first genetic risk score was built to index adiposity associated with favourable metabolic profile [51], while the second was associated with adiposity associated with an unhealthy metabolic profile [66]. Results indicated that both genetic risk scores were associated with depression, leading the authors to conclude that both favorable and unfavorable adiposity are associated with depression. This study is a clear example of how treating depression as a unity and not considering its heterogenous nature might hinder our effort to understand its biological underpinning in relation to obesity. Other genetics studies reported specific and different profiles of overlap between obesity, immuno-metabolic dysregulations and depression when considering depression heterogeneity. These studies showed that depression expressing atypical energy-related symptoms was associated with the genetic risk scores (GRS) that related to a higher risk of adiposity (i.e., genetic risk scores of BMI) and its related immuno-metabolic dysregulations (e.g., GRS of C reactive protein CRP and GRS of leptin) [69]. Two large scale studies by the UK Biobank [70] and in Psychiatric Genomics Consortium (PGC) [71] found a genetic overlap between adiposity related traits such as BMI, leptin and CRP levels and MDD with atypical energy-related symptoms such as increased appetite, weight and sleep). Moreover, these metabolic dysregulations have been hypothesized to be the link between depression and cardiovascular disease. For example, genetic instruments for immuno-metabolic dysregulations traits commonly linked to CVD, such as triglyceride, IL-6, and CRP, were associated with higher risk of depression [72]. Particularly, genetic variants that predict increased IL-6 were associated with fatigue and sleep alterations [73].

Thesis objectives

In the present thesis, we aimed to disentangle the nature of the relationship between obesity, depression and cardiometabolic diseases. We characterized the association of different measures of obesity and commonly related metabolic dysregulations with depression. Furthermore, we investigated whether this association varied across different depressive symptoms profiles. We also examined the role of metabolic dysregulation as potential linking mechanism between obesity and a depressive profile characterized by atypical symptoms

reflecting energy homeostasis. Finally, we intended to study further the effect of overall depression and specific depressive symptoms profiles on the risk of developing the cardiometabolic diseases.

OUTLINE OF THIS THESIS

Figure 1 illustrates the outline of this thesis. In **chapter two** of this thesis, we aspired to gain more knowledge about the previously reported relationship between obesity and depression by studying the association of four adiposity measures (BMI and total body fat reflecting overall adiposity, and waist circumference and visceral adipose tissue reflecting the abdominal adiposity) with overall depression scores and individual symptoms of depression measured by IDS-SR30 in participants from a population-based cohort (Netherlands Epidemiology of Obesity (NEO) study). In **chapters three and four,** we aimed to identify plasma metabolites associated with depression. We did this in two large-scale studies with two different metabolomics platforms measuring more than 1000 metabolites with a limited overlap (N=18 metabolites) in nine and five Dutch and European cohorts, respectively, from the general population and clinical settings. In **chapter five,** we considered to identify depression dimensions associated with increased risk of adverse metabolic profile by combining data on metabolomics and depressive symptoms. We performed data-driven clustering based on both symptoms and metabolomics in participants diagnosed with clinical depression. In order to replicate our findings, we examined the association between the identified dimensions and the same metabolomics panel and individual cardiometabolic risk markers (e.g., fasting glucose, insulin resistance, total body fat, and visceral adipose tissue) in an independent population-based cohort. In **chapter six**, we use genetics to separate the effect of adiposity from that of metabolic dysregulations to examine whether the link between obesity and atypical energy-related depressive symptoms is dependent on the presence of metabolic dysregulations. Finally, in **chapter seven,** we examined the effect of overall depression and specific depressive symptoms profiles on the risk of eveloping the cardiometabolic diseases. We performed a time to event analysis to disentangle the risk of overall depression and atypical energy-related symptom profile and cardiometabolic diseases and their components (type 2 diabetes and cardiovascular disease) in a median follow-up of 7 years. In **chapter eight**, we discussed the results of this thesis, methodological considerations, suggestions for future work, and the clinical implication of the thesis findings.

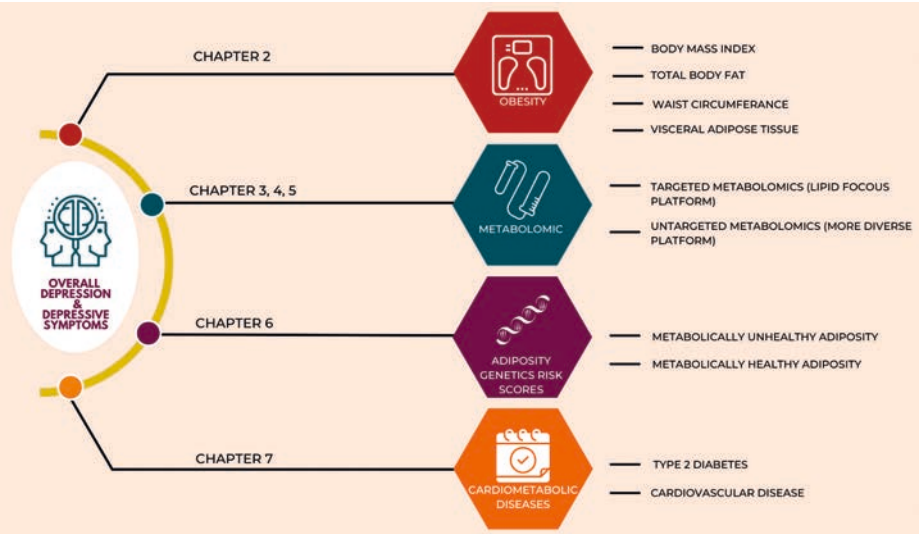

Figure 1. Outline of the thesis

Overview of the used data sources

The Netherlands Epidemiology of Obesity (NEO) study

In chapters two to seven we analysed data from *The Netherlands Epidemiology of Obesity* (NEO) study, a population-based cohort study including 6671 men and women aged 45 to 65 years [45]. All inhabitants with a self-reported body mass index (BMI) of 27 kg/m^2 or higher and living in the greater area of Leiden, the Netherlands were eligible to participate in the NEO study. In addition, all inhabitants aged between 45 and 65 years from one adjacent municipality (Leiderdorp, the Netherlands) were invited to participate irrespective of their BMI, allowing for a reference distribution of BMI. Prior to the study visit, participants completed questionnaires at home with respect to demographic, lifestyle, and clinical information. Participants visited the NEO study center after an overnight fast for an extensive physical examination including anthropometry. The present analyses are cross-sectional analyses (i.e., chapter two to six) of the baseline measurements of the NEO study and longitudinal analysis (chapter seven) of the baseline measurement of NEO study and the developing of cardiometabolic diseases extracted from GP registration in 2018. The NEO study was approved by the medical ethics committee of Leiden University Medical Center (LUMC) and all participants gave written informed consent.

Netherlands Study of Depression and Anxiety

In chapters, three, five, and six, we analysed data from *Netherlands Study of Depression and Anxiety* (NESDA), which is an ongoing longitudinal cohort study

that aims to describe the long-term course and consequences of depression and to examine its interaction with biological and psychosocial factors [82]. At baseline (n = 2981) individuals aged 18 through 65 years with depressive and/or anxiety disorders and healthy controls were included from the community, primary care, and secondary care settings between 2004 and 2007. The assessment included a diagnostic interview to assess the presence of depressive and anxiety disorders, a medical exam, and several questionnaires on symptom severity, other clinical characteristics and lifestyle. Participants were followed-up during four biannual assessments. The research protocol of NESDA was approved by the medical ethical committees of the following participating universities: Leiden University Medical Center (LUMC), Vrije University Medical Center (VUMC), and University Medical Center Groningen (UMCG).

BBMRI-NL Metabolomics Consortium

In chapter three, we analysed data from Biobanking and BioMolecular resources Research Infrastructure-The Netherlands (BBMRI-NL) with data on depression and metabolites for over 25,000 people. In addition to the described above NEO study and NESDA, data from Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) [74], The Maastricht Study [84], Erasmus Rotterdam Family study (ERF) [75], Leiden University Migraine Neuro-Analysis (LUMINA) [76], Netherlands Twin Register (NTR) [77], the Rotterdam Study (RS) [78], and Lifelines Deep (LLD) [79-81] was also included. Detailed information on these cohorts is provided in the Supplementary Materials of chapter three. All participants provided written informed consent. Studies were approved by local ethics committees.

Additional study cohorts

In chapter four, the association analysis of metabolite levels with depression was estimated in more than 13000 participants separately recruited in five different cohort studies. The following cohort studies were included: the Rotterdam Study (RS) [82], the Study of Health in Pomerania (SHIP-TREND) [83], the Cooperative Health Research in the Region of Augsburg (KORA) study [84], the European Prospective Investigation into Cancer (EPIC)-Norfolk Study [85], in addition to the Netherlands Epidemiology of Obesity (NEO) study described above. Detailed information on these cohorts is provided in the Supplementary Materials of chapter four. All participants provided written informed consent, studies were approved by their local ethics committees and conformed to the principles of the declaration of Helsinki.

REFERENCES

1. Hidaka, B.H., *Depression as a disease of modernity: explanations for increasing prevalence.* J Affect Disord, 2012. **140**(3): p. 205-14.
2. Kelly, T., et al., *Global burden of obesity in 2005 and projections to 2030.* Int J Obes (Lond), 2008. **32**(9): p. 1431-7.
3. Moore, M.E., A. Stunkard, and L. Srole, *Obesity, social class, and mental illness. 1962.* Obes Res, 1997. **5**(5): p. 503-8.
4. de Wit, L., et al., *Depression and obesity: a meta-analysis of community-based studies.* Psychiatry Res, 2010. **178**(2): p. 230-5.
5. Lucas, C.P., et al., *Insulin and blood pressure in obesity.* Hypertension, 1985. **7**(5): p. 702-6.
6. Frasure-Smith, N. and F. Lespérance, *Reflections on depression as a cardiac risk factor.* Psychosom Med, 2005. **67 Suppl 1**: p. S19-25.
7. Anderson, R.J., et al., *The prevalence of comorbid depression in adults with diabetes: a meta-analysis.* Diabetes Care, 2001. **24**(6): p. 1069-78.
8. Khawaja, I.S., et al., *Depression and coronary artery disease: the association, mechanisms, and therapeutic implications.* Psychiatry (Edgmont), 2009. **6**(1): p. 38-51.
9. Cui, Y., et al., *Prospective association between depressive symptoms and stroke risk among middle-aged and older Chinese.* BMC Psychiatry, 2021. **21**(1): p. 532.
10. Association, A.P., *American Psychiatric Association, Diagnostic and statistical manual of mental disorders (DSM-5®)*. 2013: Washington, DC.
11. Roth, G.A., et al., *Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study.* Journal of the American College of Cardiology, 2020. **76**(25): p. 2982-3021.
12. *Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019.* Lancet, 2020. **396**(10258): p. 1223-1249.
13. Luppino, F.S., et al., *Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies.* Arch Gen Psychiatry, 2010. **67**(3): p. 220-9.
14. *DEPRESSION A Global Public Health Concern* Available from: https://www.who.int/mental_health/management/depression/who_paper_depression_wfmh_2012.pdf.
15. *World Heart Federation: Mental health action plan 2013–2020. 2013.*; Available from: https://www.who.int/publications/i/item/9789241506021.
16. Malhi, G.S. and J.J. Mann, *Depression.* Lancet, 2018. **392**(10161): p. 2299-2312.
17. Möller, H.J., *Standardised rating scales in psychiatry: methodological basis, their possibilities and limitations and descriptions of important rating scales.* World J Biol Psychiatry, 2009. **10**(1): p. 6-26.
18. Rush, A.J., et al., *The Inventory of Depressive Symptomatology (IDS): psychometric properties.* Psychol Med, 1996. **26**(3): p. 477-86.

19. Smith, R.L., et al., *Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease.* Endocr Rev, 2018. **39**(4): p. 489-517.

20. *Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee.* World Health Organ Tech Rep Ser, 1995. **854**: p. 1-452.

21. Novack, D.H., et al., *Psychosomatic medicine: the scientific foundation of the biopsychosocial model.* Acad Psychiatry, 2007. **31**(5): p. 388-401.

22. Milaneschi, Y., et al., *Depression and obesity: evidence of shared biological mechanisms.* Mol Psychiatry, 2019. **24**(1): p. 18-33.

23. Faith, M.S., P.E. Matz, and M.A. Jorge, *Obesity-depression associations in the population.* J Psychosom Res, 2002. **53**(4): p. 935-42.

24. Milaneschi, Y., et al., *Depression Heterogeneity and Its Biological Underpinnings: Toward Immunometabolic Depression.* Biol Psychiatry, 2020. **88**(5): p. 369-380.

25. Zimmerman, M., et al., *How many different ways do patients meet the diagnostic criteria for major depressive disorder?* Compr Psychiatry, 2015. **56**: p. 29-34.

26. Fried, E.I. and R.M. Nesse, *Depression sum-scores don't add up: why analyzing specific depression symptoms is essential.* BMC Med, 2015. **13**: p. 72.

27. Harald, B. and P. Gordon, *Meta-review of depressive subtyping models.* J Affect Disord, 2012. **139**(2): p. 126-40.

28. Novick, J.S., et al., *Clinical and demographic features of atypical depression in outpatients with major depressive disorder: preliminary findings from STAR*D.* J Clin Psychiatry, 2005. **66**(8): p. 1002-11.

29. Khan, A.Y., et al., *Clinical and demographic factors associated with DSM-IV melancholic depression.* Ann Clin Psychiatry, 2006. **18**(2): p. 91-8.

30. Lamers, F., et al., *Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression.* Mol Psychiatry, 2013. **18**(6): p. 692-9.

31. Chu, A.L., et al., *Longitudinal association between inflammatory markers and specific symptoms of depression in a prospective birth cohort.* Brain Behav Immun, 2019. **76**: p. 74-81.

32. Beijers, L., et al., *Biomarker-based subtyping of depression and anxiety disorders using Latent Class Analysis. A NESDA study.* Psychol Med, 2019. **49**(4): p. 617-627.

33. Osimo, E.F., et al., *Longitudinal population subgroups of CRP and risk of depression in the ALSPAC birth cohort.* Compr Psychiatry, 2020. **96**: p. 152143.

34. Lamers, F., et al., *Depression profilers and immuno-metabolic dysregulation: Longitudinal results from the NESDA study.* Brain Behav Immun, 2020. **88**: p. 174-183.

35. Milaneschi, Y., et al., *The association between plasma tryptophan catabolites and depression: The role of symptom profiles and inflammation.* Brain Behav Immun, 2021. **97**: p. 167-175.

36. Milaneschi, Y., et al., *Leptin Dysregulation Is Specifically Associated With Major Depression With Atypical Features: Evidence for a Mechanism Connecting Obesity and Depression.* Biol Psychiatry, 2017. **81**(9): p. 807-814.

37. Lamers, F., et al., *Metabolic and inflammatory markers: associations with individual depressive symptoms.* Psychol Med, 2018. **48**(7): p. 1102-1110.

38. Jokela, M., et al., *Inflammation and Specific Symptoms of Depression.* JAMA Psychiatry, 2016. **73**(1): p. 87-8.

39. Lasserre, A.M., et al., *Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study.* JAMA Psychiatry, 2014. **71**(8): p. 880-8.

40. Sethi, S. and E. Brietzke, *Omics-Based Biomarkers: Application of Metabolomics in Neuropsychiatric Disorders.* Int J Neuropsychopharmacol, 2015. **19**(3): p. pyv096.

41. Pereira-Miranda, E., et al., *Overweight and Obesity Associated with Higher Depression Prevalence in Adults: A Systematic Review and Meta-Analysis.* J Am Coll Nutr, 2017. **36**(3): p. 223-233.

42. Quek, Y.H., et al., *Exploring the association between childhood and adolescent obesity and depression: a meta-analysis.* Obes Rev, 2017. **18**(7): p. 742-754.

43. Jung, S.J., et al., *Association between body size, weight change and depression: systematic review and meta-analysis.* Br J Psychiatry, 2017. **211**(1): p. 14-21.

44. Hebebrand, J., et al., *A Proposal of the European Association for the Study of Obesity to Improve the ICD-11 Diagnostic Criteria for Obesity Based on the Three Dimensions Etiology, Degree of Adiposity and Health Risk.* Obes Facts, 2017. **10**(4): p. 284-307.

45. *Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies.* Lancet, 2004. **363**(9403): p. 157-63.

46. de Mutsert, R., et al., *The Netherlands Epidemiology of Obesity (NEO) study: study design and data collection.* Eur J Epidemiol, 2013. **28**(6): p. 513-23.

47. Xu, Q., D. Anderson, and J. Lurie-Beck, *The relationship between abdominal obesity and depression in the general population: A systematic review and meta-analysis.* Obes Res Clin Pract, 2011. **5**(4): p. e267-360.

48. Vogelzangs, N., et al., *Depressive symptoms and change in abdominal obesity in older persons.* Arch Gen Psychiatry, 2008. **65**(12): p. 1386-93.

49. Goossens, G.H., *The Metabolic Phenotype in Obesity: Fat Mass, Body Fat Distribution, and Adipose Tissue Function.* Obes Facts, 2017. **10**(3): p. 207-215.

50. Gómez-Zorita, S., et al., *Metabolically healthy obesity and metabolically obese normal weight: a review.* J Physiol Biochem, 2021. **77**(1): p. 175-189.

51. Ji, Y., et al., *Genome-Wide and Abdominal MRI Data Provide Evidence That a Genetically Determined Favorable Adiposity Phenotype Is Characterized by Lower Ectopic Liver Fat and Lower Risk of Type 2 Diabetes, Heart Disease, and Hypertension.* Diabetes, 2019. **68**(1): p. 207-219.

52. Yaghootkar, H., et al., *Genetic Evidence for a Link Between Favorable Adiposity and Lower Risk of Type 2 Diabetes, Hypertension, and Heart Disease.* Diabetes, 2016. **65**(8): p. 2448-60.

53. Huang, L.O., et al., *Genome-wide discovery of genetic loci that uncouple excess adiposity from its comorbidities.* Nat Metab, 2021. **3**(2): p. 228-243.

54. Pescatello, L.S., *Exercise Prescription and Management for Cardiometabolic Health.* ACSM's Health & Fitness Journal, 1999. **3**(2): p. 15-21.

55. Sattar, N., et al., *Can metabolic syndrome usefully predict cardiovascular disease and diabetes? Outcome data from two prospective studies.* Lancet, 2008. **371**(9628): p. 1927-35.

56. Mezuk, B., et al., *Depression and type 2 diabetes over the lifespan: a meta-analysis.* Diabetes Care, 2008. **31**(12): p. 2383-90.

57. Wium-Andersen, M.K., et al., *An attempt to explain the bidirectional association between ischaemic heart disease, stroke and depression: a cohort and meta-analytic approach.* Br J Psychiatry, 2020. **217**(2): p. 434-441.

58. Holmes, M.V., et al., *Causal effects of body mass index on cardiometabolic traits and events: a Mendelian randomization analysis.* Am J Hum Genet, 2014. **94**(2): p. 198-208.

59. Polsky, D., et al., *Long-term risk for depressive symptoms after a medical diagnosis.* Arch Intern Med, 2005. **165**(11): p. 1260-6.

60. Penninx, B.W., et al., *Understanding the somatic consequences of depression: biological mechanisms and the role of depression symptom profile.* BMC Med, 2013. **11**: p. 129.

61. Nicholson, J.K., J.C. Lindon, and E. Holmes, *'Metabonomics': understanding the metabolic responses of living systems to pathophysiological stimuli via multivariate statistical analysis of biological NMR spectroscopic data.* Xenobiotica, 1999. **29**(11): p. 1181-9.

62. Zheng, H., et al., *Predictive diagnosis of major depression using NMR-based metabolomics and least-squares support vector machine.* Clin Chim Acta, 2017. **464**: p. 223-227.

63. Shao, W.H., et al., *Combined Metabolomics and Proteomics Analysis of Major Depression in an Animal Model: Perturbed Energy Metabolism in the Chronic Mild Stressed Rat Cerebellum.* Omics, 2015. **19**(7): p. 383-92.

64. Paige, L.A., et al., *A preliminary metabolomic analysis of older adults with and without depression.* Int J Geriatr Psychiatry, 2007. **22**(5): p. 418-23.

65. Gadad, B.S., et al., *Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks.* J Affect Disord, 2018. **233**: p. 3-14.

66. Tyrrell, J., et al., *Using genetics to understand the causal influence of higher BMI on depression.* Int J Epidemiol, 2019. **48**(3): p. 834-848.

67. Davey Smith, G. and G. Hemani, *Mendelian randomization: genetic anchors for causal inference in epidemiological studies.* Hum Mol Genet, 2014. **23**(R1): p. R89-98.

68. Igo, R.P., Jr., T.G. Kinzy, and J.N. Cooke Bailey, *Genetic Risk Scores.* Curr Protoc Hum Genet, 2019. **104**(1): p. e95.

69. Milaneschi, Y., et al., *Polygenic dissection of major depression clinical heterogeneity.* Mol Psychiatry, 2016. **21**(4): p. 516-22.

70. Badini, I., et al., *Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-metabolic traits and alcohol consumption.* Psychol Med, 2020: p. 1-11.

71. Milaneschi, Y., et al., *Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations.* JAMA Psychiatry, 2017. **74**(12): p. 1214-1225.

72. Khandaker, G.M., et al., *Shared mechanisms between coronary heart disease and depression: findings from a large UK general population-based cohort.* Mol Psychiatry, 2020. **25**(7): p. 1477-1486.

73. Milaneschi, Y., et al., *Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts.* Mol Psychiatry, 2021. **26**(12): p. 7393-7402.

74. van Greevenbroek, M.M., et al., *The cross-sectional association between insulin resistance and circulating complement C3 is partly explained by plasma alanine aminotransferase, independent of central obesity and general inflammation (the CODAM study).* Eur J Clin Invest, 2011. **41**(4): p. 372-9.

75. Schram, M.T., et al., *The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities.* Eur J Epidemiol, 2014. **29**(6): p. 439-51.

76. van Oosterhout, W.P., et al., *Validation of the web-based LUMINA questionnaire for recruiting large cohorts of migraineurs.* Cephalalgia, 2011. **31**(13): p. 1359-67.

77. Boomsma, D.I., et al., *Netherlands Twin Register: from twins to twin families.* Twin Res Hum Genet, 2006. **9**(6): p. 849-57.

78. Hofman, A., et al., *The Rotterdam Study: 2016 objectives and design update.* Eur J Epidemiol, 2015. **30**(8): p. 661-708.

79. Scholtens, S., et al., *Cohort Profile: LifeLines, a three-generation cohort study and biobank.* Int J Epidemiol, 2015. **44**(4): p. 1172-80.

80. Tigchelaar, E.F., et al., *Gut microbiota composition associated with stool consistency.* Gut, 2016. **65**(3): p. 540-2.

81. Zhernakova, A., et al., *Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity.* Science, 2016. **352**(6285): p. 565-9.

82. Ikram, M.A., et al., *Objectives, design and main findings until 2020 from the Rotterdam Study.* Eur J Epidemiol, 2020. **35**(5): p. 483-517.

83. Völzke, H., et al., *Cohort profile: the study of health in Pomerania.* Int J Epidemiol, 2011. **40**(2): p. 294-307.

84. Holle, R., et al., *KORA--a research platform for population based health research.* Gesundheitswesen, 2005. **67 Suppl 1**: p. S19-25.

85. Day, N., et al., *EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer.* Br J Cancer, 1999. **80 Suppl 1**: p. 95-103.