Disentangling the relationship between depression, obesity and cardiometabolic disease

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Discussion

DISCUSSION

Brief introduction of the main aims and findings

Obesity, depression and cardiometabolic diseases are complex phenotypes [1, 2]. Their heterogeneity complicates studying them individually and hinders efforts to understand the links between them. This thesis aimed to elucidate the relationship between obesity and depression and possible mechanisms linking both conditions together and with cardiometabolic diseases.

Figure 1 in chapter 1 illustrates the outline of this thesis. First, our aim in **chapter two** of this thesis was to examine the relationship between obesity and depression in N=6459 participants. We uniquely dissected both obesity and depression in our analysis. Instead of relying only on body mass index (BMI), we used it together with three other adiposity measures. Two of the four measures reflect the overall adiposity (BMI and total body fat), and the other two reflect the abdominal adiposity (waist circumference and visceral adipose tissue). For the depression side, we assessed 30 depressive symptoms (IDS-SR30). We found that all four measures of adiposity were positively associated with depressive mood and individual symptoms of depression. Furthermore, this link between measures of adiposity (particularly total body fat) and depressive symptoms appeared to be more robust for atypical energy-related depressive symptoms (increased weight, increased appetite, low energy level and leaden paralysis).

Second, to identify plasma metabolites associated with depression, in **chapters three and four**, we performed two studies with two different metabolomics platforms measuring more than 1000 metabolites with a limited cross-platform overlap (N=18 metabolites). The first and the second metabolomics studies used data from, respectively, nine (total N=15 428) and five (total N= 13 596) Dutch and European cohorts from the general population and clinical settings. In **chapter three**, by using a targeted lipid-based metabolomics platform, we found a metabolic signature for depression characterized by twenty-one lipids, fatty acids, and low-molecular-weight metabolites: as compared to non-depressed controls, participants with depressed mood had lower levels of high-density lipoprotein (HDL), short-chain fatty acid and ketone body acetate and higher levels of very low-density lipoprotein (VLDL), triglyceride particles, glycoprotein acetyls, tyrosine and isoleucine. Associations were generally consistent across sex, age, and BMI strata and across cohorts assessing depression diagnoses with psychiatric interview versus those assessing depressive symptoms with self-report instruments. Furthermore, in **chapter four,** leveraging a wide untargeted metabolomic platform, we identified 53 metabolites associated with depression, including those in the monoamine and neurotransmitter pathways (serotonin, kynurenate and glutamate). These associations were partially explained by

antidepressant use (i.e., a possible proxy for depression severity). We also identified novel associations for retinol (vitamin A), 1-palmitoyl-2-palmitoleoyl-GPC (16:0/16:1) (lecithin), and lower levels of 2-aminooctanoate, 10-undecenoate (11:1n1), 1-linoleoyl-GPA (18:2) with depression. These novel associations were not explained by antidepressant use, cardiovascular medication and lifestyle factors.

Next, in **chapter five**, we extended the use of the same metabolomic platform applied in chapter three to investigate depression heterogeneity. We performed a data-driven clustering analysis based on depressive symptoms and metabolomics in N=1094 participants diagnosed with clinical Major Depressive Disorder (MDD) (i.e., in the last six months) from the Netherlands Study of Depression and Anxiety (NESDA). We aimed to identify depression dimensions associated with an adverse metabolic profile. Clustering analysis identified the following two metabolite-depression dimensions. The first dimension was characterized by a substantially uniform endorsement of mood, cognitive, and somatic depressive symptoms and lower levels of metabolic dysregulations. The second is a dimension with relatively stronger contribution from energy-related behavioral symptoms (such as sleeping too much, increased appetite, and low energy levels) and increased levels of metabolic dysregulations. After the clustering step, we examined the association between these dimensions and the same metabolomics panel and individual components of cardiometabolic diseases (fasting glucose levels, insulin resistance, total body fat, and visceral adipose tissue) in N=6572 participants from the NEO study. The first depression dimension was associated with a lower cardiometabolic risk profile. In contrast, the dimension with relevance for energy-related depressive symptoms was associated with higher visceral adipose tissue, triglyceride levels, branched-chain amino acids, glycoprotein acetylase, insulin resistance and lower HDL-cholesterol levels.

In chapter six, we investigated whether the established link between adiposity and atypical energy-related symptoms of depression is rooted in underlying metabolic dysregulations. In this analysis, we uncoupled the effect of adiposity from that of metabolic dysregulations in relation to atypical energy-related symptoms profile by studying the relationships between two previously defined adiposity increasing genetic risk scores (GRS) and atypical energy-related symptoms profile. Both genetic instruments used in this study were associated with increased body fat. The difference between them was that one genetic risk score was associated with the predisposition to an unfavorable metabolic profile (i.e., metabolic dysregulations), whereas the other was associated with a favorable metabolic profile. We meta-analyzed results from two individual studies; the NEO study (N= 5734) and NESDA (N= 2238). We found that higher atypical energy-related depressive symptoms was positively and specifically associated with GRS that increased the risk of adiposity accompanied by metabolic dysregulations,

but not with the GRS of obesity with a favorable metabolic profile; these findings suggest that metabolic dysregulation represents a connecting mechanism between adiposity and atypical energy related symptoms of depression.

Finally, in **chapter seven**, we explored the association between different depressive symptom profiles and the risk of development of cardiometabolic diseases in N= 6561 individuals from the NEO study, over a median follow-up of seven years. We were able to disentangle the components of the exposure (depressive symptoms categorized in overall depression and atypical energy-related symptoms profile) and the outcome (cardiometabolic diseases categorized as type 2 diabetes and cardiovascular disease). We found that overall depression was associated with an increased risk of cardiometabolic disease. More specifically, the atypical energy-related symptoms profile was significantly associated with an increased risk of type 2 diabetes onset.

Insights based on the main findings

The results of this thesis render two major insights. First, the interrelatedness between obesity and depression goes deeper than distal factors such as social stigma, self-image, or the use of medication and lifestyle, since our analysis reported an overlap between metabolic signatures in depression and obesity that was not fully explained by these factors. We hypothesized that metabolic dysregulation is a potential biological candidate that could (at least partially) explain the comorbidity between obesity and depression (see The potential role of metabolic dysregulation in the link between obesity and depression section). Second, the connection between depression, metabolic dysregulation and obesity varied due to depression heterogeneity and was strongest for a specific depressive symptom profile. We found that metabolic dysregulations correlated more consistently with atypical energy-related symptoms profile. This symptoms profile was positively associated with adiposity only in the presence of metabolic dysregulations. Depression heterogeneity also impacted the link between depression and cardiometabolic diseases with atypical energy-related symptoms profile increasing specifically the risk of type 2 diabetes.

The potential role of metabolic dysregulation in the link between obesity and depression

Many interconnected biological pathways can explain how metabolic dysregulation links obesity and depression and how the two conditions can further lead to cardiometabolic diseases. Firstly, it is possible that obesity causes depression, mediated through inflammation, insulin resistance, and metabolic dysregulation. Previous molecular epidemiological studies (i.e., Mendelian Randomization) suggested a causal role of obesity in developing depression [3]. Similarly, another recent Mendelian randomization suggested a causal role of obesity in

increased C-reactive protein (CRP) levels [4]. Inflammation has been shown to impact on psychopathological processes relevant for depression, alterations in monoaminergic neurotransmission, tryptophan degradation towards neurotoxic end-products, glutamate-related increased excitotoxicity, decreased neurotrophic factors synthesis or hypothalamic-pituitary-adrenal(HPA)-axis activity disruption [5]. Inflammation may also alter the function of two closely connected hormones (leptin and insulin) giving rise to insulin resistance [6] and leptin resistance [7]. Leptin is secreted proportional to the body's adiposity and is known, along with insulin, as the "fed state" hormones [8, 9]. Both hormones have receptors in the hypothalamus, the area of the brain responsible for maintaining the overall body homeostasis, which, if compromised, is linked with depression [10, 11]. Longitudinally, elevated acute phase cytokines and proteins in the baseline increased the risk of developing depressive symptoms [12, 13]. Also, CRP interferes with leptin binding with its receptor leading to leptin resistance [14]. Leptin resistance causes elevated leptin concentrations, which in turn inhibits insulin secretion from pancreatic β cells [15].

Impairment of insulin function is linked to metabolic dysregulation that may lead to depression. A wide range of metabolic dysregulations, such as disrupted lipid and glucose metabolism, has frequently been reported in obesity and depression [10, 16-18]. This is in line with results from our metabolomic-depression analysis (chapters three and four), where we used two large scales metabolomic platforms to investigate the metabolic signature of depression. For example, we reported increased VLDL, triglyceride, and lower HDL cholesterol. These findings show an overlap between metabolic signatures in both obesity [19] and depression.

Secondly, another possibility is the reverse, i.e., that depression causes obesity, mediated by metabolic dysregulation. Adulthood and early life stress cause depression that may intervene with food choices, physical activity, and metabolic homeostasis leading to dyslipidemia, inflammation, and metabolic dysregulation. Alterations in circulating lipid concentrations may be linked to pathophysiological pathways related to depression and obesity, such as chronic activation of the hypothalamic-pituitary-adrenal (HPA) axis or chronic low-grade inflammation [20]. Glucocorticoid-induced hypercortisolemia is known to result in lipolysis, the release of fatty acids and synthesis of very-low density lipoprotein (VLDL) [21]. Similarly, activation of the pro-inflammatory response leads to a reduction in HDL cholesterol and phospholipids, and an increase in triglyceride, caused by the compensatory production and accumulation of phospholipid-rich VLDL [22]. From metabolomic-depression analysis (chapters three and four), we found that lower levels of high-density lipoprotein (HDL), short-chain fatty acid and ketone body acetate and higher levels of very low-density lipoprotein (VLDL), triglyceride particles, glycoprotein acetyls, tyrosine, and vitamin A were associated with

depression. Vitamin A has previously been suggested as a cause of dyslipidemia by increasing the synthesis of triglyceride-rich very-low-density lipoproteins (VLDLs), inhibiting fatty acid degradation, and affecting the synthesis of apolipoproteins in the liver [23, 24].

Lastly, a common cause could influence both depression and obesity. Carrying a genetic disposition to leptin and insulin resistance independently or with a genetic predisposition for inflammation may precede and give rise to metabolic dysregulation, leading to both obesity and depression. Leptin stimulates the appetite-suppressing [25] proopiomelanocortin (POMC) neuron in the nucleus of the hypothalamus that activates the transcription of the melanocortin peptides (i.e., α, β, and γ MSH, and Mc3r and Mc4r) [26]. It has been proposed [27] that alterations of the leptin–melanocortin pathway impair not only its anorexigenic effect, leading to obesity, but also its effect on mood regulation, potentially leading to the development of depression. A recent study [28] identified five shared genetic risks between depression (or its treatment) and obesity. Two of these genes are components of the leptin-melanocortin pathway (i.e., proopiomelanocortin (POMC) and brain-derived neurotrophic factor (BDNF)). The link between obesity and metabolic dysregulation through leptin resistance and further depression may explain our findings from chapter two. We reported a positive association between depression and total body fat. Symptoms of depression related to disturbance of energy homeostasis were associated with total body fat (see below 'Heterogeneity of depression and obesity'). This result is in line with the previous work that examined the relationship between adiposity and depression (by using BMI as a proxy for total body fat) in epidemiological studies [10, 29-31]. Thus, metabolic dysregulation may act in two non-mutually exclusive ways: as a common underlying factor influencing the liability to both depression and obesity or as mediating mechanism in causal relationships between these conditions [10].

Heterogeneity of depression and obesity

We confirmed the existence of different dimensions within the construct of depression rooted in partially divergent underlying biological and genetic mechanisms. In this thesis, we observed that the link between obesity and depression was more apparent when considering the heterogeneity of depression and obesity. Similarly, the association of depression with cardiometabolic diseases changed as a function of depression heterogeneity. We found from the results of chapter two that depressive symptoms related to energy homeostasis were relatively more strongly linked to total body fat (i.e., adiposity) as compared to other symptoms. From the results of chapter six, we found that atypical energy-related symptoms profile was positively associated with the genetic variants that increased the predisposition to increase total body fat with metabolic dysregulation but not with the genetic variants that increased the predisposition to

obesity without metabolic dysregulation. This aligns with the recently introduced transdiagnostic model of immuno-metabolic depression (IMD) [32], suggesting that inflammatory and metabolic dysregulations act as a shared substrate influencing the development of specific behavioral symptoms common to depression and obesity. For instance, as mentioned above, alterations in central signaling of leptin and insulin may associate with shifting body energy balance from expenditure to accumulation. This shift favors the development of hyperphagia, present in both obesity and atypical energy-related form of depression. Previous research [33] has shown that among patients with a current diagnosis of depression, higher leptin concentration in the blood is associated with depressive symptoms related to energy metabolism like hyperphagia, fatigability and physical exhaustion, independently from BMI. This agrees with our results from chapter two, where we reported that the effect estimates for symptoms of this cluster were the top-ranked for the associations between individual depressive symptoms with total body fat (i.e., closely linked to leptin concentration). Additionally, our results from chapter five, where we performed a data-driven clustering analysis between metabolites commonly associated with cardiovascular health and depressive symptoms, show the presence of a specific dimension with higher relative relevance for symptoms like difficulty falling asleep, sleeping too much, increased appetite, and low energy level correlates with metabolic dysregulations. These metabolic dysregulations have been hypothesized to link depression and cardiometabolic diseases. For example, immuno-metabolic dysregulations such as marked by elevated plasma concentrations of triglycerides, IL-6, and CRP, were causally related to depression [34]. Interestingly, a recent study has shown that inflammation as measured by IL-6 activity but not CRP is a potential cause for a specific symptoms profile of depression, such as sleep problems or fatigue [35]. Finally, our findings suggest that metabolic dysregulation links obesity and depression with some but not all elements of cardiometabolic diseases. For example, atypical energy-related symptoms profile was specifically related to an increased risk of type 2 diabetes but not cardiovascular disease.

Future work

We suggest three important areas of research in this field for the coming years. Firstly, more longitudinal studies that aim to study the relationship between depression symptoms profile and obesity and cardiometabolic diseases are needed to understand the directionality of the reported associations. Second, experimental mechanistic studies and genetically informed designs such as Mendelian Randomization may identify the presence of causal processes underlying these associations. Finally, future randomized control trials aiming to target the underlying immuno-metabolic dysregulations via pharmacological or behavioral interventions (such as exercising, dieting and sleep hygiene) in patients with depression expressing atypical energy-related symptoms are needed to help

us understand to what extent treating underlying metabolic dysregulation will contribute to mitigate this symptoms profile adversity.

Methodological considerations

Several methodological aspects of this thesis should be considered. The main strength of the analysis of this thesis is using data from two large and deeply phenotyped cohorts. The NEO study has detailed information about obesity phenotype with additional information about depression, and the NESDA has detailed depression phenotype with additional information about obesity. Both cohorts have the same depressive symptoms instruments, lipid-related metabolomic data, and obesity-related genetics that allowed us to perform discovery-replication and pooled analysis in the two cohorts. However, some methodological limitations should be acknowledged. First, the observational nature of the analyses in this thesis does not allow us to completely rule out the possibility of residual confounding. However, due to the design of the cohorts, we could adjust for a broad set of relevant confounding factors related to the studies' associations, including age, sex, educational level, smoking, alcohol consumption, physical activity, antidepressants, lipid-lowering drugs, and ethnicity. Second, most of the studies of this thesis were performed in a cross-sectional design which does not allow us to infer causality in the detected associations. Third, we cannot rule out the possibility of reverse causality due to the nature of observational studies in chapter seven, where we performed a longitudinal analysis between baseline depressive symptoms profiles and developing type 2 diabetes and cardiovascular disease. However, we consider this highly unlikely, mainly because we removed participants with cardiometabolic diseases at the baseline. Fourth, in the NEO study, the depressive symptoms were assessed only via the self-report IDS-SR30 without a clinical diagnosis of depression. Nonetheless, IDS-SR30 is time and cost-efficient for research purposes and showed high concordance with the clinical diagnosis of depression [36].

The implication of this work

This thesis adds to the existing knowledge that encourages the consideration of a more refined classification for depression based on depressive symptoms profiles and their possible biological underpinnings. Albeit healthcare providers are shifting from assessing adiposity solely based on BMI by incorporating waist circumference and lipid profile to diagnose the overall health profile, less has been done so far regarding depression heterogeneity. It is essential to increase awareness about the different manifestations of depression symptomatology, which may arise from potentially divergent pathophysiological pathways. Two individuals with the same DSM-5 scores could have completely different symptoms profiles, biological vulnerabilities and disease trajectory or prognosis. Thus, it is important that healthcare providers become aware of the link between depressive

symptom profiles and their associations with biological biomarkers related to other health problems such as obesity, insulin resistance, type 2 diabetes and cardiovascular disease. Target screening of specific symptom profiles can provide better healthcare for patients with depression. This screening can also be used to protect from, or delay, the manifestation of metabolic dysregulations to cardiometabolic diseases (i.e., type 2 diabetes and cardiovascular disease). When patients with depression are expressing atypical energy-related symptoms profile, it may be useful to monitor their metabolic health biomarkers to prevent the development of cardiometabolic diseases. Our results highlight the importance of considering the instruments to assess depressive symptoms in research and clinical practice. In most studies, psychometric instruments are used to ask about changes in neurovegetative symptoms such as appetite and sleep, but not about the direction of that change. The overwhelming majority of questionnaires assessing depressive symptoms conflate opposite changes in neurogenerative symptoms (example: one question conflating decreased and increased appetite: "Poor appetite or overeating" from UK Biobank mental health questionnaire (MHQ) [37, 38] and another question from the UK Biobank computerized touchscreen interface questionnaire [39] evaluating the presence of a change in the weight but not the direction of that change, such as loss or gain weight: "Compared with one year ago, has your weight changed?" with the following multiple choices No - weigh about the same, Yes - gained weight, Yes - lost weight, Do not know, Prefer not to answer). However, based on the results of this thesis, the connection between changes in appetite and metabolic dysregulation seems stronger for one specific direction of the changes (i.e., increased appetite and weight gain). Adding to that, refining the depression phenotype will increase the precision of the genetic studies that aim to comprehend depression genetic architecture [40]. In the clinical setting, we also should increase awareness about the correlation between depressive symptoms profiles with distinct biological and clinical manifestations when treating patients with depression. It is crucial to take a close look at the symptoms expressed in each patient. Based on the results of this thesis, we demonstrated that participants with depression expressing atypical energy-related depressive symptoms might carry genetic and clinical vulnerability to insulin-resistance related illness (i.e., adiposity, metabolic dysregulations, and type 2 diabetes). Similarly, diseases that are usually put under the label of cardiometabolic diseases should be studied separately as research has shown that each may have a partially distinct pathophysiology. The original definition of cardiometabolic diseases was used to describe the elements of metabolic syndrome and the diseases that they predict (i.e., stroke, heart disease, and type 2 diabetes). However, the definition of cardiometabolic diseases has expanded recently to include cardiovascular diseases, insulin resistance-related diseases, and renal function related diseases (example [28, 41]). Although all these conditions are closely related, it may be beneficial to distinguish groups of diseases that share similar underlying pathophysiology.

In chapter seven, we found that atypical energy-related depressive symptoms were associated with an increased risk of type 2 diabetes but not cardiovascular disease (i.e., both labelled as cardiometabolic diseases). The 2016 guidelines on cardiovascular disease prevention from The European Society of Cardiology's (ESC) [42] recommend active screening for increased cardiometabolic risk factors such as obesity, type 2 diabetes and depression starting from age 40 for men and age 50 for women at least once every five years. We argue that following up on patients with depression for cardiometabolic diseases and measuring specific depressive symptoms in individuals at risk for cardiometabolic diseases could be beneficial in primary and secondary preventive efforts. Additionally, preventive and treatment efforts may benefit from a more personalized approach taking into account differential depressive symptoms manifestations. Very recently, clinical trials [43-45] have started testing the efficacy of targeting immuno-metabolic pathways in the treatment of specific subgroups of depressed patients selected based on their bio-clinical profile. Among these clinical studies, the INFLAMED trial [45] is currently testing the efficacy of an anti-inflammatory add-on to standard antidepressants in the treatment of MDD patients expressing atypical energy-related symptoms and with sign of low-grade inflammation.

Conclusion

Our findings highlight the importance of considering the heterogeneity of adiposity, depression, and cardiometabolic diseases. The complex nature of the relationship between the three conditions makes it challenging to draw a one-size-fits-all conclusion. Our results suggest that metabolic dysregulation is a potential biological mechanism that links specific forms of depression with obesity. This proposed mechanism could lead to the development of cardiometabolic diseases. In this thesis, we found that the atypical energy-related symptoms profile - characterized by behavioral symptoms reflecting altered energy intake and expenditure (i.e., increased appetite, increased sleepiness, low energy level, leaden paralysis, increased weight) - is the main driver of the relationship between depression, adiposity, immune-metabolic dysregulation and their later manifestation (type 2 diabetes). It is important to raise awareness about the depression heterogeneity and how distinct symptoms profile such as atypical energy-related symptoms profile could further correlate with clinical manifestation of metabolic dysregulation and increase the risk of debilitating diseases such as type 2 diabetes. Future detailed genetics and experimental studies that aim to answer the causation question are needed in order to move forward to better precise and personalize diagnosis and treatment for all patients with depression, obesity and cardiometabolic diseases.

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