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## Summary and general discussion



## 9.1 SUMMARY

Depressive and anxiety disorders as well as cardiovascular disease (CVD) are highly prevalent and their major contribution to the worldwide burden of disease will continue to increase. Substantial evidence implies that depressive and anxiety disorders increase the risk of CVD. There is a growing interest in whether depression and anxiety increase the risk of metabolic adversities as well. Metabolic adversities like dyslipidemia, abdominal and overall obesity, hypertension and hyperglycemia tend to cluster in individuals as the metabolic syndrome. Because these metabolic adversities predict over half of CVD cases, they may help to explain the increased risk of CVD in depression and anxiety. So far, findings on the association of metabolic risk factors for CVD with depressive and anxiety disorders are equivocal.

It was the overarching intend of this thesis to study which characteristics (that is, disorders, severity or dimensions) of depression and anxiety make people prone to certain metabolic risk factors for CVD. The association of antidepressant use with metabolic risk factors was also examined. Moreover, the contribution of biological stress systems and lifestyle to these associations was explored. Additionally, the relationship of personality traits and childhood trauma with metabolic risk was addressed. Studies were based on the Netherlands Study of Depression and Anxiety (NESDA), a large longitudinal cohort study involving 2329 people with lifetime depressive and/or anxiety disorders and 652 healthy controls.

First, we concentrated on the question whether characteristics of depression and anxiety were cross-sectionally associated with metabolic risk factors. In **chapter 2**, it was described that, overall, people with a current major depressive disorder (MDD) and/or an anxiety disorder were not at an increased risk of the metabolic syndrome or its components as compared to controls. However, people with more severe symptoms of depression and to a lesser extent those with more severe symptoms of anxiety were at increased risk of the metabolic syndrome. This increased risk of the metabolic syndrome was driven by a higher prevalence of abdominal obesity, low high-density lipoprotein (HDL) cholesterol and elevated triglycerides. First, these findings illustrated that scales that assess the severity of symptoms of depression or anxiety better reflect individual metabolic derangements than categorical diagnoses. Therefore, severity scales allow determining more precise associations of depression and anxiety with metabolic risk. Second, these findings showed that symptoms of depression and anxiety are not related to an increased risk of the metabolic syndrome as such but to the metabolic risk factors abdominal obesity and dyslipidemia in particular. That especially the components abdominal obesity and dyslipidemia are related to depression and anxiety may explain the mixed findings of previous research on the whole metabolic syndrome in depression or anxiety.

Another finding was that users of tricyclic antidepressants (TCAs) were prone towards abdominal obesity, hypertriglyceridemia and hypertension. This was independent of depressive symptoms, and therefore may reflect TCA-specific side effects.

In **chapter 3** the focus was on the cross-sectional association of dyslipidemia with depression and anxiety. HDL cholesterol levels were lower, and triglyceride levels higher in people with a current MDD than in those with a remitted MDD or controls. People with more severe symptoms of depression had higher levels of total and low-density lipoprotein (LDL) cholesterol and of triglyceride and lower levels of HDL cholesterol and were thus prone towards dyslipidemia.

Whether specific depression and anxiety symptom dimensions of the tripartite theoretical model related specifically to metabolic risk factors was explored in **chapter 4**. Somatic arousal was, independent of lifestyle factors, associated with increased abdominal obesity, triglyceride levels and blood pressure.

Longitudinal associations of depression and anxiety with metabolic risk factors were addressed in **chapter 5**. More severe symptoms of depression and anxiety at baseline predicted a decrease in HDL cholesterol levels and an increase of abdominal obesity over the subsequent 2 years. A reduction of symptoms of depression and anxiety over this time period was not related to amelioration of lipid or abdominal obesity values. This indicated that people who are vulnerable to symptoms of depression or anxiety may display a progression of dyslipidemia and abdominal obesity rather than a decline, even if they have an improvement in mood state. If depression or anxiety were directly related to dyslipidemia and obesity, one would expect that fluctuations in mood state would go together with similar fluctuations in lipid and obesity values. Since such convergence was not objectified, it was concluded that severe symptoms of depression or anxiety may not be directly related to dyslipidemia and abdominal obesity. Rather stable etiological factors – such as sustained smoking, unhealthy diets, inflammation or shared genetic substrates – may connect them.

As described above, people with more severe symptoms of depression and anxiety as well as TCA users were at increased risk of dyslipidemia and of abdominal and overall obesity. Subsequently, it was investigated whether biological stress systems and lifestyle contributed to these cross-sectional associations. Associations of the autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis with metabolic risk were portrayed in **Chapter 6**. Increased sympathetic nervous system (SNS) and decreased parasympathetic nervous system (PNS) activity but not basal HPA axis functioning were related to the metabolic syndrome and all of its components. This indicated that ANS dysfunctioning but not HPA axis dysregulation relates to metabolic risk.

In **chapter 7** it was reported that elevated levels of the systemic inflammatory marker C-reactive protein (CRP) as well as smoking

substantially explained the increased prevalence of dyslipidemia and obesity among people with more severe symptoms of depression or anxiety. ANS dysregulations additionally contributed to the metabolic risk among TCA users. ANS dysregulations may be a side effect of TCAs. These findings enhance our understanding of the mechanisms behind the increased risk of dyslipidemia and obesity in depressive and anxiety disorders. Because these putative pathways did not completely explain dyslipidemia or (abdominal) obesity among severely depressed or anxious people, other contributors (e.g., dietary or genetic factors) to these associations remain to be identified.

In **chapter 8** the relation of Big Five personality traits (i.e., extraversion, openness, agreeableness, neuroticism and conscientiousness) and childhood trauma type (i.e., emotional neglect, and psychological, physical or sexual abuse) with metabolic risk factors was additionally studied. Less openness as well as sexual abuse during childhood were independently associated with lower HDL cholesterol and with abdominal obesity. In addition, less openness was related to a higher blood pressure.

Altogether, the findings of chapters 2 through 8 indicate that symptom severity measures of depression and anxiety are more strongly and consistently related to metabolic risk than disorder classifications. Moreover, it was shown that more severe symptoms of depression and anxiety were related to progressive dyslipidemia and obesity but not to hypertension or hyperglycemia. Low-grade systemic inflammation as well as smoking partly contributed to these associations. The use of TCAs was related to an increased risk of dyslipidemia, obesity and hypertension, partly due to enhanced sympathetic and decreased parasympathetic ANS activity. Somatic arousal, childhood sexual abuse and less openness were associated with an increased metabolic risk as well.

If future research confirms these findings, this may help to identify the particular patients who are at a high risk of metabolic adversities and thereby of CVD, and indicate that screening and treatment of metabolic risk factors may be of benefit. Moreover, the factors that contributed to these associations (that is, smoking, inflammation and ANS imbalance) may facilitate the development of new and more fundamental treatment options to reduce CVD risk in patients with depressive or anxiety disorders.

## **9.2 GENERAL DISCUSSION**

In this general discussion the main findings of this thesis will be reviewed, which may contribute to a more comprehensive theory of the role of depression and anxiety in metabolic risk. Also, methodological considerations, and potential implications for future research and clinical practice will be delineated.

### **9.2.1 THE METABOLIC SYNDROME AND ITS COMPONENTS**

The metabolic syndrome has been hypothesized to connect depression and anxiety with CVD. Consequently, several former studies investigated the relationship of depression or anxiety with the whole metabolic syndrome rather than with its individual metabolic components.

However, debate exists whether the metabolic syndrome is a valid concept.<sup>116-309</sup> A first point of criticism is that the metabolic syndrome might be too heterogeneous to define it as a single disorder: combinations of metabolic risk factors vary considerably between individuals. Second, probably no single pathophysiological mechanism underlies the metabolic syndrome. That makes it difficult to develop one treatment that can beneficially affect all components of the metabolic syndrome. A third subject of debate is that the metabolic syndrome does not seem to add to the prediction of CVD beyond the contribution of each individual component. To compare our findings with previous research we studied the metabolic syndrome in relation to depression and anxiety. But because of the questioned validity of the metabolic syndrome concept, we also focused on the relative importance of its individual components.

The findings of this thesis underscore the criticism that the metabolic syndrome may be too heterogeneous to define it as a single disorder. We observed that people with symptoms of depression or anxiety were at increased risk of the metabolic syndrome. However, this increased risk of the metabolic syndrome was driven by a higher prevalence of (abdominal) obesity, low HDL cholesterol and elevated triglycerides (i.e., dyslipidemia) only. Those people were not prone towards hypertension or hyperglycemia. Symptoms of depression and anxiety do thus not necessarily relate to the metabolic syndrome as a whole but only to some specific components. Our findings do not stand alone. Earlier studies that focused on all metabolic syndrome components also mainly reported associations of depression and anxiety with dyslipidemia and obesity,<sup>20-30, 43-46</sup> and more seldom with hypertension<sup>21,27</sup> or hyperglycemia.<sup>22,43,45</sup> Because depression and anxiety are especially related to (abdominal) obesity and dyslipidemia, associations with the whole metabolic syndrome could be weakened. This may explain the mixed findings of previous research on the metabolic syndrome in depression or anxiety.

Why are dyslipidemia and obesity but not hypertension or hyperglycemia associated with depression and anxiety? Maybe etiological factors associated with depression and anxiety such as smoking, inflammation and a sedentary lifestyle mainly affect lipid and obesity

values. Further, core symptoms of depression such as changes in appetite, a loss of energy and reduced initiative (inducing a sedentary lifestyle) may primarily stimulate dyslipidemia and obesity. The other way around, obesity may cause pain in overloaded joints<sup>143</sup> and a lower self-esteem through weight-related prejudices,<sup>310</sup> and therefore induce symptoms of depression.

In sum, compelling evidence exists that symptoms of depression and anxiety are particularly associated with dyslipidemia and obesity rather than with all metabolic syndrome components. As a consequence, we recommend that future studies focus on the individual metabolic risk factors and not (only) on the metabolic syndrome as a whole in relation to depression and anxiety. This approach will clarify the relative importance of individual metabolic risk factors in relation to depression and anxiety.

## **9.2.2 PSYCHOLOGICAL INDICATORS OF METABOLIC RISK**

### **9.2.2.1.1 Severity of depression and anxiety and metabolic risk**

It is invaluable to determine which characteristics of depression and anxiety are most strongly associated with an increased metabolic risk. Subsequently, such information may help to improve prevention and intervention programs.

Various previous studies examined whether depressive or anxiety disorders were related to metabolic risk. Some of these studies reported that depressive or anxiety disorders were related to metabolic adversities, while others did not find such an association. We also did not consistently find that depressive or anxiety disorders were associated with an increased overall metabolic risk. Results of studies on metabolic risk in depressive or anxiety disorders are thus ambiguous.

Patients with a disorder are commonly compared to those without the disorder. Reasons for this approach are that it eases comparability to previous research, that disorder concepts are simplified, and that studies match cut-off points that are used in clinical practice.

However, persons differ in their quantity of symptoms of depression or anxiety. Consequently, symptoms of depressive and anxiety disorders are gradually distributed within the general population without a clear cut-off between people with or without a disorder.<sup>311</sup> By classification into diagnostic groups such variation in symptom severity is not taken into account, which may result in a loss of valuable information.

Considerable methodological literature demonstrates the negative consequences of dichotomizing gradual, continuous variables within scientific research (see for example: <sup>162,312,313</sup>). The loss of variation causes a drop in effect sizes and in power. This increases the risk of not finding a significant result when the effect actually is present (that is, type 2 error). This may explain why studies on metabolic risk that categorize subjects in those with and without dichotomous depressive or anxiety disorders yielded inconsistent results.

In this thesis, associations of metabolic risk with severity of depressive or anxiety symptoms were indeed more consistent and robust than those with diagnosis groups. Likewise, an earlier study reported that severity of depressive symptoms tended to be associated with abdominal obesity and significantly related to lower HDL cholesterol levels. But associations between the presence or absence of a depressed mood and metabolic risk factors were not observed.<sup>25</sup>

The importance to define psychological state as a continuous measure is increasingly recognized. The fact that in developing the new, fifth version of the international Diagnostic and Statistical Manual (DSM-V) of mental disorders, there is high global interest in incorporating a dimensional component into the existing categorical binary classification system underscores this tendency.

A comment should be added to our findings. NESDA participants were recruited from general practices and outpatient mental health care. Patients with the most severe depressive and anxiety disorders who are admitted to inpatient mental health care were therefore not part of our sample. As a result, our findings cannot be generalized to the most severely depressed and anxious patients. It is conceivable that inpatients through more severe and complex psychopathology are more vulnerable to dyslipidemia and (abdominal) obesity than outpatients. Alternatively, inpatients may have a higher risk of weight loss and malnutrition which may reduce body weight and total cholesterol levels. Studies that address these associations among inpatients have however been much more scarcely reported. In an extension of NESDA, inpatients have been recruited.<sup>314</sup> Studies on metabolic risk in depression and anxiety within this sample are underway. These will clarify whether our findings also apply to a more severely depressed and anxious inpatient population.

#### **9.2.2.1.2 The contribution of smoking and inflammation**

Understanding mechanisms linking depression and anxiety to dyslipidemia and obesity could provide opportunities for prevention and intervention. What factors may have contributed to the liability towards dyslipidemia and obesity in people with more severe symptoms of depression and anxiety?

First, the tendency towards dyslipidemia in people with more severe symptoms of depression or anxiety was substantially explained by smoking. This might be because they started smoking easier, possibly because of shared (e.g., genetic) etiological factors.<sup>197</sup> Moreover, people with symptoms of depression or anxiety may have had less motivation to quit. This is inherent to the lack of motivation accompanying their disease, but there is also evidence that nicotine has antidepressant effects.<sup>197,198</sup> Smoking is thought to increase total and LDL cholesterol as well as triglyceride levels and to lower HDL cholesterol<sup>75,97</sup> and hence is an important target in the management of dyslipidemia.<sup>17</sup> Moreover, smoking is strongly linked to other adverse lifestyle factors like increased saturated



fat, cholesterol and alcohol intake<sup>315</sup> that may exacerbate dyslipidemia. In sum, smoking importantly relates to depression and anxiety as well as to dyslipidemia. It is thus plausible that smoking partly explained the increased risk of dyslipidemia in people with severe symptoms of depression or anxiety.

Elevated serum levels of the systemic inflammation marker CRP additionally explained the increased risk of dyslipidemia and of obesity in people with more severe depressive or anxiety symptoms. It is known that people with depressive<sup>72</sup> or anxiety disorders<sup>73</sup> display higher levels of inflammatory markers among which CRP. In turn, inflammation may induce dyslipidemia. Inflammatory factors stimulate the release of lipids into the bloodstream to provide energy for host defense. At the same time, inflammation causes a reduction in HDL lipoproteins, resulting in a decreased reverse cholesterol transport.<sup>51</sup> Adipose tissue cells react to these signals by releasing inflammatory markers themselves.<sup>257</sup> Thereby, adipose tissue additionally promotes dyslipidemia in a vicious circle relationship. Elevated CRP levels might also lead to obesity. It is thought that circulating CRP binds to leptin, through which the action of leptin is reduced (which is called 'leptin resistance').<sup>201,202</sup> The hormone leptin controls appetite after eating. Leptin resistance leads to insufficient suppression of appetite and therefore to increased food intake. This may ultimately lead to obesity.

To sum up, inflammation is linked to depression and anxiety on the one hand and to dyslipidemia and obesity on the other hand. It is therefore conceivable that increased inflammation in people with symptoms of depression or anxiety partly explained their vulnerability to dyslipidemia and obesity. Moreover, since smoking substantially raises CRP levels,<sup>260</sup> smoking could have partly induced the increased inflammation in depression and anxiety.

Yet, smoking and inflammation did not fully explain dyslipidemia and obesity among people with more severe symptoms of depression or anxiety. A complexity of factors is eligible as linking mechanism between depression and anxiety on the one hand and lipids and body fat on the other hand. Therefore, probably multiple factors underlie the liability towards dyslipidemia and obesity among people with symptoms of depression and anxiety.

Our longitudinal findings also supported the idea that depression and anxiety were not directly related to dyslipidemia and obesity, but could be due to various underlying factors. If depression or anxiety were directly related to dyslipidemia and obesity, one would expect that fluctuations in mood state over time would go together with similar fluctuations in lipid and obesity values. However, an improvement in mood over time did not coincide with reductions of dyslipidemia or obesity. Dyslipidemia and abdominal obesity even aggravated. This indicates that rather stable etiological factors in people who are vulnerable to symptoms of depression or anxiety cause a progression of dyslipidemia and abdominal obesity,

independent of ameliorations in mood state. From a broader perspective, our longitudinal results are in line with the finding that treatment of depression does not ameliorate the prognosis of existent CVD.<sup>316-317</sup> This observation further stresses the need to gain insight into the mechanisms that are responsible for persistent poor cardiovascular outcomes in depression and anxiety.

Another factor that could further contribute to progressive dyslipidemia and obesity is that people who are vulnerable to depression or anxiety, independent of their current mental state, continue to eat less healthy with more carbohydrates and saturated fat.<sup>118</sup> Persistent unhealthy dietary habits may lead to increases in dyslipidemia and obesity. Moreover, it is possible that symptoms of depression and anxiety share genetic substrates with HDL cholesterol and abdominal obesity. For instance, complex gene-environment interactions may have activated the HPA axis, which subsequently has led to depression as well as to aggravation of obesity. Another possibility is that depressed and anxious people are less healthy in general. In this thesis only CVD and diabetes mellitus were taken into account, and these conditions did not explain the associations found. But several other chronic conditions like renal disease, rheumatoid arthritis and chronic obstructive pulmonary disease are related to depression or anxiety<sup>318-320</sup> as well as to metabolic risk factors.<sup>321-323</sup> Hence, it is conceivable that depression and anxiety are accompanied by a poorer overall health status,<sup>324</sup> which more robustly induces dyslipidemia and obesity.

Research has only just begun to unravel the mechanisms that underlie metabolic risk in depression and anxiety. Besides measurement error and random fluctuations, other factors than smoking and inflammation could account for the unexplained variance in the associations of dyslipidemia and obesity with more severe symptoms of depression and anxiety. However, the precise role of these factors remains to be elucidated by future research. The identification of these factors is essential as these could provide additional leads to better prevent and treat dyslipidemia and obesity in depression and anxiety.

### **9.2.2.2 TCA use and metabolic risk**

Patients who used TCAs were at an increased risk of dyslipidemia, abdominal and overall obesity and hypertension, which could be side effects of TCAs. These findings fit well with the growing evidence of adverse effects of TCAs.<sup>58-63</sup> In secondary care, TCAs are commonly prescribed by psychiatrists. A detailed understanding of their side effects is important to be able to adequately weigh the metabolic risks and the benefits of TCA prescription against alternative treatments. Our findings also stress the importance to monitor for metabolic risk during TCA treatment.

We found that an increased SNS and decreased PNS activity of the ANS as well as increased systemic inflammation partly explained the tendency towards dyslipidemia and obesity in users of TCAs. A higher rate

of smokers among TCA users additionally explained part of their vulnerability towards dyslipidemia. Previous research already indicated such an ANS imbalance and inflammation as TCA side-effects. It has been found that TCAs are agonists for the peripheral  $\alpha_1$  adrenergic receptors,<sup>63</sup> which trigger sympathetic activation of the ANS. This sympathetic response may have induced dyslipidemia and obesity, and also vasoconstriction which increases blood pressure. TCAs also have other adverse effects on the cardiovascular system. Their use has also been associated with a decreased parasympathetic control of the heart by the vagus nerve.<sup>62,244</sup> This reduced cardiac vagal control lowers the variability in heart rate. Such beat-to-beat fluctuations in the rhythm of the heart are however essential for good cardiac health. For that reason, reduced heart rate variability (HRV) predicts greater cardiac mortality.<sup>325</sup> Increased systemic inflammation was also observed as a side effect in a former study,<sup>60</sup> although the mechanism that underlies an inflammatory response to TCAs is still poorly understood.

Our findings also showed that higher smoking rates among TCA users explained part of their dyslipidemia. Maybe TCA users initially had a more severe form of depression and were therefore more likely to smoke. This may have confounded their tendency towards dyslipidemia. Depressed NESDA participants on TCAs did not display higher depression severity scores than those free of TCAs, but this is probably attributable to efficacy of TCAs. According to treatment guidelines, TCAs should only be prescribed after unsuccessful administration of SSRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs).

ANS dysregulation, inflammation and smoking did not entirely explain associations of TCA use with dyslipidemia, obesity or hypertension. Probably other factors are also involved. One such a factor may be antihistaminergic effects of TCAs, which may induce weight gain<sup>58,59</sup> and subsequently dyslipidemia.<sup>131</sup> Another possibility is the abovementioned probability that TCA users initially have more severe and longer lasting symptoms of depression. These severe and prolonged symptoms together with possible side effects of previously used antidepressants may have amplified their metabolic risk.

### **9.2.3 CAUSAL PATHWAYS OF METABOLIC RISK IN DEPRESSION AND ANXIETY**

How can we be sure that depression and anxiety lead to metabolic disturbances? Is there a possibility that this association also runs in the opposite direction? In other words, can metabolic disturbances lead to symptoms of depression or anxiety as well? Insight into cause and consequence of these conditions is still limited. Such knowledge is essential to determine the direction of preventive and therapeutic strategies. Our longitudinal information made it possible to add to the literature on the direction of possible causality.

We assumed that depression preceded dyslipidemia and obesity. The reason for this assumption is that key symptoms of depression are a change in appetite or weight. Moreover, depression and anxiety are often accompanied by unhealthy lifestyle changes. Furthermore, it is thought that depression and anxiety are associated with dysregulated biological stress systems. This could adversely affect lipid levels and body fat. In our longitudinal analyses, more severe symptoms of depression or anxiety at baseline predicted a worsening of dyslipidemia and obesity over time. This finding supports our assumption that depression and anxiety precede dyslipidemia and obesity. Additional evidence for this temporal sequence is derived from meta-analyses that showed that depression preceded obesity.<sup>195,326</sup>

The reverse causal route that dyslipidemia and obesity cause depression or anxiety is plausible as well. Although a genetic study reported that the apolipoprotein E genotype which anchors basal cholesterol levels did not determine depression scores,<sup>40</sup> another study reported that dyslipidemia did predispose to depression.<sup>106</sup> Moreover, a meta-analysis<sup>195</sup> as well as later studies<sup>327,328</sup> showed that obesity increases the risk of future depression. For instance weight-based discrimination<sup>310</sup> could cause feelings of depression. Other evidence for reverse causation comes from a large prospective cohort study which reported that a Mediterranean diet – which is preventive for dyslipidemia and obesity – protects against depression.<sup>247</sup>

Taken together, it is likely that the association of dyslipidemia and obesity with depression and anxiety runs in two directions. Depression and anxiety on the one hand and dyslipidemia and obesity on the other hand might reinforce each other in a vicious cycle.

Because no definite conclusions can be drawn from the relatively scarce studies on longitudinal associations of metabolic risk with depression and anxiety, there lays a major challenge for future research to investigate the possibility of bidirectional causation. In NESDA we studied whether symptoms of depression or anxiety preceded dyslipidemia or obesity. To verify the hypothesis of bidirectionality, it would be compelling to investigate within NESDA data whether lipid or obesity levels predict symptoms of depression or anxiety as well. In addition, replication of longitudinal research on these causal pathways within other longitudinal data collections as well as in treatment trials is warranted.

#### **9.2.4 CLINICAL AND FUTURE RESEARCH IMPLICATIONS**

Health research in the past decades has increasingly focused on the interplay between mental and physical health, of which this thesis is an example. This research field more and more indicates that mental difficulties like depression and anxiety are associated with an array of adverse physical outcomes among which diabetes mellitus and CVD. Still, in clinical practice a division exists between the care for mental and physical illnesses. In the care of people with depression or anxiety, there is

not yet a systematic approach to detect and treat co-morbid physical conditions. Within this patient group, physical conditions may therefore progress unnoticed into severe physical ailments. In line with the growing scientific evidence, our findings further stress the need to implement physical care in mental health care. Better awareness in mental care for physical jeopardies could eventually reduce morbidity and mortality rates associated with co-morbid physical conditions such as CVD.

The main finding delineated in this thesis is that severe symptoms of depression and to a lesser extent of anxiety are associated with an increased risk of dyslipidemia and (abdominal) obesity. Because depression and anxiety are among the most common mental disorders, general practitioners (GPs) and especially mental health care professionals regularly treat patients with severe symptoms of depression or anxiety. They could therefore play an important role in reducing the risk of dyslipidemia and obesity and ultimately of CVD among this patient group.

Although weight loss frequently occurs in people with depression, weight gain (with obesity and dyslipidemia as end points) is also regularly observed in patients with depression. Although weight gain might be seen as a normal consequence of depression and of certain antidepressant medication use, clinicians should become more aware of the increased CVD morbidity and mortality associated with weight gain and related dyslipidemia.

In future research, it should be determined whether screening for dyslipidemia and obesity in severely depressed or anxious patients is effective. Severity of depressive and anxiety symptomatology could among others be assessed by the Inventory of Depressive Symptoms (IDS) and the Beck Anxiety Questionnaire (BAI). The IDS and BAI were applied in NESDA and are valid and internationally applied severity scales for depression and anxiety that take little time. We found that people with an IDS score from 49 or a BAI score from 30 displayed a significantly increased risk of dyslipidemia or obesity. Although these thresholds are arbitrary and need to be verified, they provide an indication for cut-off scores for research on dyslipidemia and obesity screening.

When patients report severe symptoms of depression or anxiety higher than the abovementioned threshold, it may be recommendable that GPs and psychiatrists assess their fasting lipid profile and their degree of obesity. The leading dyslipidemia guideline<sup>97</sup> advises dyslipidemia screening in adults at increased risk of CVD at least five-yearly. Overall and abdominal obesity should be assessed during intake and regularly thereafter. A body mass index (BMI [ $\text{kg}/\text{m}^2$ ]) of over 25.0,<sup>57</sup> and a waist circumference (WC) of > 102 cm in men or > 88 cm in women<sup>17</sup> are the most widely accepted indicators of overall and abdominal obesity.

If dyslipidemia or obesity is present, diminution of smoking and inflammation might reduce these conditions. Smoking cessation already is generally recommended to reduce dyslipidemia and inflammation,<sup>17, 97</sup> and this general recommendation may facilitate implementation. The most

promising way to reduce smoking dependence within this specific patient group is an integrated behavioral and pharmacological approach combined with psychological counseling of depression or anxiety.<sup>329</sup> Such smoking cessation programs should focus on short-term goals, like building up self-efficacy and motivation to quit, and then stimulating gradual abstinence.<sup>330</sup>

Of course, prevention is the best cure. In severely depressed or anxious patients without obesity or dyslipidemia, clinicians should focus on primary prevention of these conditions, because subsequent weight loss and reduction of dyslipidemia through for example quitting smoking are more difficult to accomplish. This could be achieved by sensitizing patients to the health risks associated with obesity and dyslipidemia and detrimental lifestyle habits like smoking, and through encouraging self-care and self-monitoring in terms of lifestyle and weight.<sup>331</sup>

Future research should determine whether reduction or prevention of smoking and inflammation really reduces the risk of dyslipidemia and obesity among severely depressed or anxious people. If proven effective, screening people with more severe symptoms of depression or anxiety for dyslipidemia and obesity and subsequent prevention and modification strategies could become part of multidisciplinary guidelines and thereby help preventing CVD. Current general<sup>332,333</sup> and mental health care guidelines<sup>334,335</sup> only advice to assess whether or not a depressive or anxiety disorder is present. The assessment of anxiety and depression severity should then be additionally included into these guidelines.

Other strategies could also beneficially affect dyslipidemia and obesity in people with more severe symptoms of depression or anxiety. Physical activity and weight reduction are both recommended to reduce dyslipidemia,<sup>97</sup> obesity<sup>17</sup> and inflammation.<sup>17</sup> Physical activity further has the advantage that it may help to improve mood,<sup>336</sup> at least in the short term.<sup>337</sup> Guided running therapy is therefore already included in international guidelines for treatment of mild to severe depression.<sup>334,338</sup> In the future it should be examined whether for example stimulating physical activity adds to dyslipidemia and obesity management in this specific patient group.

Another finding of this thesis was that TCA users had an increased risk of dyslipidemia, obesity and hypertension. Severity of depression did not explain these results, and so these metabolic disturbances could reflect side effects of TCAs. Therefore, clinicians should be reticent about prescribing TCAs. However, TCAs are usually prescribed after other kinds of antidepressants or psychological interventions have failed to sufficiently relieve symptoms of depression or anxiety. TCA use is thus one of the last resorts, and the few alternatives also have contraindications and side effects.<sup>334</sup> When there are no better alternatives, it should therefore be considered whether, for example based on TCA blood levels, a lowest effective dose can be determined. Furthermore, screening TCA users for

dyslipidemia, obesity and hypertension at the intake and regularly thereafter could be important.

Taken together, the findings in this thesis and related literature underscore that patients reporting severe symptoms of depression or anxiety should be considered as a population at increased risk of dyslipidemia and obesity. The close relationship of depression and anxiety with dyslipidemia and obesity may justify a more integrated clinical approach. Future research should further verify these associations, and whether actions aimed at prevention, detection and management of dyslipidemia and obesity are of benefit. Such actions may ultimately reduce CVD morbidity and mortality in people with depression and anxiety.

### **9.2.5 METHODOLOGICAL CONSIDERATIONS**

Specific limitations of the studies presented in this thesis were already addressed in the corresponding chapters. One of the overarching limitations comprised the limited ability to conclude about causality because of the observational and mainly cross-sectional nature of our studies. A second limitation encompassed the unavailability of additional explanatory information such as information about diet.

In this General discussion, some additional considerations were attended to. A first consideration was that due to attrition the most severely depressed and anxious people were not optimally represented within the NESDA study. As a result, the findings of this thesis are not merely generalizable to those most severely ill. The degree of generalization to this specific population could however be clarified by data of NESDA inpatients.<sup>314</sup> A related restriction is that only adults aged 18 through 65 were included in NESDA. This stands in the way the generalizability of our findings to the elderly. In the future, our findings could be verified in elderly within the Netherlands Study of Depression in Older persons (NESDO)<sup>339</sup>, which was designed largely comparable to NESDA.

A final consideration was that the increased metabolic risk among TCA users might not just be a reflection of adverse TCA effects. TCAs are normally prescribed only after unsuccessful treatment with SSRIs and SNRIs. Therefore, TCA users could have been a subgroup with initially more severe and longer lasting symptoms of depression. These severe and prolonged symptoms together with possible side effects of previously used antidepressants may have contributed to their increased metabolic risk.

### **9.2.7 GENERAL CONCLUSION**

The aim of this thesis was to clarify which aspects of depression and anxiety are related to an increased metabolic risk, and which factors contribute to these associations. Taken together, our findings indicate that people with more severe symptoms of depression and anxiety are at particular risk of progressive dyslipidemia and (abdominal) obesity. The higher rates of smoking and systemic inflammation among people with depression or anxiety partially accounted for their adverse metabolic

profile. Dysregulations of the autonomic nervous system partly explained why users of tricyclic antidepressants displayed an increased risk of dyslipidemia and (abdominal) obesity as well, and also of hypertension. These important findings shed light on useful avenues for future research, and on preventive and therapeutic insights and directions.



