8.

General Discussion

DISCUSSION

The aim of this thesis was threefold: (1) to investigate whether parasympathetic and sympathetic nervous system dysfunction are related to depression and anxiety disorders, (2) to examine whether antidepressants affect this relationship, and (3) whether ANS activity is associated with metabolic abnormalities and in particular the metabolic syndrome.

In the current chapter, the main findings of Chapters 2 through 7 will be shortly summarized. Subsequently, the results will be discussed within the framework of outcomes of previous studies. In addition, where possible, the contribution of these findings to a more general theory about cardiac autonomic functioning in depression and anxiety is addressed. Finally, some methodological considerations will be addressed, topics for future research are described, and possible clinical implications of the findings of this thesis will be reviewed.

Table 1. Main Results of Chapter 2 through 6 on the Association between Autonomic Functioning and Depression and Anxiety

	Psychopathology, antidepressant naïve		Antidepressants		
	Major Depressive Disorder	Anxiety Disorders	TCAs	SNRIs	SSRIs
Cross-sectional					
RSA	-/x[a]	x	-	-	-
SDNN	x	x	-	-	-
Heart rate	x	x	+	+	-
Blood pressure	-/x[b]	+/x[c]	+	+	x
PEP	x	+	+	+	-
Longitudinal					
RSA	x	x	-	-	-
Heart rate	x	x	+	+	-

PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; SDNN, standard deviation of normal-to-normal interval; SNRI, serotonergic and noradrenergic working antidepressant; SSRI, selective serotonin re-uptake inhibitor; TCA, tricyclic antidepressant.
Explanation of marks: -, negative association; +, positive association; x, no association
[a] Significant negative association for rest condition, but not for test condition
[b] Significant negative association with systolic blood pressure, but not with diastolic blood pressure
[c] Significant positive association with diastolic blood pressure, but not with systolic blood pressure

Table 1 summarizes the results of Chapter 2 through 6. Results of Chapter 7 are not presented in this figure but will be discussed at the end of this section.

Do MDD or anxiety disorders dysregulate autonomic activity?

Parasympathetic activity in depression

When antidepressant use is not considered, cross-sectional analyses showed that depression is associated with decreased heart rate variability measures (RSA and SDNN), but not with heart rate (**Chapter 2**). However, when antidepressant use was introduced as a confounder or when heart rate variability measures were compared between controls and antidepressant naïve depressed persons, associations between heart rate variability and MDD diminished to non-significant or only weak associations were found (Chapter 2). Although these small effects may suggest that there is a limited intrinsic effect of MDD on cardiac parasympathetic activity, analysis of the longitudinal data provided no support for a causal relationship between depression and cardiac vagal tone or heart rate (**Chapter 4**).

A meta-analysis of Rottenberg (2007[1]) revealed a weak association between depression and cardiac vagal control with a small to medium effect size. Only three out of the 13 reviewed studies found a significant association and this precisely pictures the literature on this subject: Results are inconsistent and provide no coherent image of parasympathetic activity in depression[2-5]. In addition, Rottenberg suggested that antidepressants may have a significant impact on autonomic function and should be considered when the relationship between depression and vagal tone is studied. Several studies indeed reported decreases in parasympathetic activity after antidepressant treatment[6-9]. Results of other studies that addressed antidepressant use were rather inconclusive, but tended to find no association between depression and parasympathetic control of the heart[2,5,10-12]. In sum, the results of previous studies as well as the outcomes of the present thesis suggest no or only a weak association between antidepressant-naïve MDD and cardiac vagal control.

Parasympathetic activity in anxiety

Antidepressant-corrected cross-sectional analyses performed in the present study pointed out that neither RSA, SDNN, nor heart rate is associated with anxiety disorders (**Chapter 3**). Longitudinal analyses confirmed the absence of a link: No causal relationship is found between anxiety disorders and RSA and heart rate (Chapter 4).

Our findings are in contrast with those reported by Friedman (2007[13]) and Cohen (2006[14]). Both authors reviewed several small studies on parasympathetic

control in anxiety disorders and concluded that the results - although heterogeneous - point to a small reduction in cardiac vagal control in different anxiety disorders[15-17]. However, it should be noted that some studies found no association between anxiety disorders and cardiac vagal tone[12,18] or even reported increased vagal tone in anxious patients[19]. Thus, although most of the previous studies did stratify for or did exclude antidepressant use and results therefore concern associations with anxiety disorders itself, no consistent solid evidence for decreased PNS activity in anxiety disorders was found. The cross-sectional and longitudinal results presented in the present thesis are in line with this view.

Sympathetic activity in depression

In **Chapter 5**, it was shown that persons with MDD display lower systolic blood pressure than controls (after correction for antidepressant use) in the absence of an effect on the heart rate. Examination of differences in cardiac sympathetic drive as measured by the pre-ejection period (PEP), revealed that depression (after correction for antidepressant use) is not associated with cardiac sympathetic control (**Chapter 6**). Several other studies report decreased blood pressure in depressed subjects as well.[20-23] The one previous study that investigated the association between PEP and depression[20] found a positive correlation between PEP and depression, suggesting decreased cardiac sympathetic activity. In short, none of the current results supports the hypothesis that depression is associated with <u>increased</u> cardiac SNS activity.

Previous studies that assessed sympathetic activity in depression employing non-cardiac-specific measures such as norepinephrine (NE) spillover and skin conductance levels (SCL) have yielded more variable results. Most of these studies reported moderate increases in SNS activity in depression[7,24,25], although some studies did not reveal any relationships[6,26]. It should be noted that increased levels of NE in depressed subjects do not by necessity lead to cardiac changes measured by PEP, heart rate and SBP (as found in Bruno *et al.* and seen in Chapters 5 and 6). Several studies suggest that beta-adrenergic activity or number of beta-receptors is decreased in depression[20,27-29]. This means that an increased sympathetic drive may be hidden by a decrease of the effectiveness of the target organs to respond to adrenergic drive. A fair summary is that the evidence for increased SNS activity in depression is currently not convincing, but can also not be ruled out.

Sympathetic activity in anxiety

Anxiety disorders are associated with a minor increase in diastolic blood pressure, when adjusted for antidepressants, but this effect was not observed for systolic blood pressure (Chapter 5). Although these findings may indicate increased vascular SNS activity, an opposite effect was seen in cardiac sympathetic control as measured by the PEP: Compared to control subjects, anxious persons not taking antidepressants had a longer PEP signalling lower SNS control (Chapter 6). Since PEP can be prolonged by increased afterload[30-32], we adjusted the mean PEP for mean arterial pressure (as a proxy for aortic pressure)[1,2,6,13,24] and found that the high PEP in currently anxious persons was reduced to non-significant. In line with the high DBP seen in these subjects (which is also considered a proxy for aortic pressure/afterload), this suggests that a high afterload obscured the actual relationship and unjustly suggested decreased SNS control in anxious persons. Taken together, these results do not provide strong evidence for a change in cardiac sympathetic activity in anxiety.

Other studies that investigated sympathetic activity in anxiety disorders employed different measures such as low frequency heart rate variability (LF, which is suggested to reflect cardiac sympathetic activity[33], but has also been reported not to show the expected correlation with PEP[34]) and SCL and very heterogeneous results were reported[12,17-19,35,36]. Most of these studies accounted for antidepressant use (e.g. by employing a washout period) but used relatively small sample sizes that may have restrained the ability to control for important confounders and therefore may have contributed to the inconclusive findings. In short, these studies do not show a consistent or strong association between anxiety disorders and sympathetic tone, in full keeping with our own results.

Do antidepressants dysregulate autonomic activity?

Parasympathetic activity and antidepressant use

Both cross-sectional (Chapter 2 and 3) and longitudinal analyses (Chapter 4) revealed that all types of antidepressants were associated with a significant decrease in vagal tone. TCAs most strongly affected PNS activity, followed by SNRIs and SSRIs. On the other hand, when the use of antidepressants was discontinued, vagal activity returned almost to normal levels.

In contrast to the fact that no robust association was found between

cardiac vagal control and depression and anxiety, the research on the relationship between antidepressant use and parasympathetic control of the heart is reasonably solid in providing evidence for a diminished PNS activity in patients who use TCAs or SNRIs. Van Zyl *et al.* (2008[8]) and Sala *et al.* (2009[37]) reviewed many small studies that reported measures of cardiac vagal tone, mainly before and after treatment with different antidepressants, which were all associated with decreased heart rate variability. Effects of SSRIs on parasympathetic activity are less distinct and consistent. Several studies reported no vagal effects after administration of SSRIs[38, 39], whereas other studies reported results similar to ours: Decreased parasympathetic activity after SSRI treatment[9, 40]. No studies investigated the reversibility of these effects. In short, research now provides firm evidence that TCAs and SNRIs reduce PNS activity. Although the results are not as robust as for TCAs and SNRIs, SSRIs also seem to reduce cardiac vagal tone, albeit to a smaller extent.

Sympathetic activity and antidepressant use

Our cross-sectional findings suggest that cardiac sympathetic activity was increased by TCAs and SNRIs, since heart rate and blood pressure were higher, and PEP was shorter in users of these antidepressants compared to non-users (Chapter 3, 5 and 6). These observations are further supported by our longitudinal results that show that the use of TCAs or SNRIs is reflected in heart rate increasing effects (Chapter 4). An opposite effect was seen for SSRIs: PEP was longer and heart rate was lower in users of SSRIs compared to antidepressant naïve persons, suggesting a decrease in sympathetic control (Chapter 3 and 6). Longitudinal analyses further demonstrate a heart rate lowering effect of SSRIs (Chapter 4). The effects of TCAs, SNRIs, and SSRIs seemed reversible to a large extent, since heart rate returned almost to normal levels when antidepressant use was stopped.

In addition, other studies (mostly with small sample size) have also shown that SNS measures are influenced by antidepressant use. Van Zyl (2008[8]) and Sala (2009[37]) showed that heart rate is increased by TCAs and SNRIs, whereas SSRIs are associated with decreased heart rate. Similar results have been reported by studies that employed SNS measures such as NE spillover and SCL: SNS activity increased after TCA and SNRI use[7,41,42] and a decrease in SNS activity was seen after SSRI use[6,43,44]. No previous studies addressed the reversibility of antidepressant effects on SNS function.

In short, although longitudinal data on sympathetic control is not available

yet, the present cross-sectional results and the findings from other studies suggest that TCAs and SNRIs increase cardiac sympathetic activity, whereas SSRIs decrease SNS activity. In addition, it seems that the major part of the vagal effects of antidepressants and almost the entire effect on sympathetic control is reversible when antidepressant use is ceased.

Potential mechanisms

Thus, it appears that antidepressants have an important effect on ANS activity and this effect may have confounded the reported relationships between ANS and depression and anxiety in previous studies that did not control for antidepressant use. How antidepressants may influence cardiac autonomic function is discussed in Chapter 4. Although mechanisms are complex and yet not clearly specified, a possible explanation is that TCAs mainly inhibit NE re-uptake, increasing the levels of NE. Through accentuated antagonism NE has a blocking effect on muscarinic receptors and TCAs may also have intrinsic anticholinergic effects that may decrease PNS activity even more[45-50]. SNRIs have the same properties as TCAs in inhibiting NE re-uptake, and therefore also increase SNS activity and, through accentuate antagonism, decrease PNS activity. However, SNRIs lack the intrinsic anticholinergic effects and may therefore show less pronounced effects than TCAs. Finally, SSRIs mainly inhibit serotonin (5-HT) re-uptake. Activation of 5-HT receptors may inhibit muscarinic receptors while increasing NE clearance, causing decreased PNS activity and SNS activity[51-57].

In conclusion, the findings of this thesis indicate that lowered parasympathetic control and increased sympathetic control over the heart seen in depressed and anxious patients are not intrinsic effects of depression and anxiety disorders per se, but are an effect induced by the antidepressants that are prescribed to a substantial part of patients with these disorders.

Does autonomic activity dysregulation result in metabolic abnormalities?

Two main stress systems, the ANS and the HPA-axis, are thought to play an important role in causing metabolic dysregulations after activation by (chronic) stress[58-62]. Although results of studies on the relationship between HPA-axis and metabolic abnormalities are quite heterogeneous, studies focusing on ANS activity show rather consistent patterns of increased sympathetic and decreased parasympathetic activity to be associated with metabolic changes such as increased

waist circumference and glucose levels[63-67]. Whether the effects of the PNS and SNS branches are independent or that a specific pattern of activation/reciprocity of the SNS and PNS is related to metabolic syndrome has not been studied before. This thesis shows that decreased vagal activity and increased sympathetic control are independently related to metabolic dysregulations such as dyslipidemia, abdominal obesity, hypertension, and hyperglycaemia and to the metabolic syndrome, but that a reciprocal effect is also seen.

Although the ANS and HPA-axis are often co-activated, and it is generally thought that the two stress systems collaborate and affect each other[68-70], none of the studies addressing metabolic dysregulation investigated possible correlations/interactions between these two systems. In **Chapter 7**, these possible intercorrelations/interactions were examined. They appeared to be non-existing since autonomic measures (RSA, PEP, and heart rate) did not correlate with HPA-axis measures (cortisol awaking response, dexamethasone suppression test, and evening cortisol). The additional finding that no relationship was found between HPA-axis activity and metabolic abnormalities indicates that the HPA-axis does not play a (moderating) role in the association between ANS and metabolic abnormalities.

How could depression and anxiety disorder cause cardiovascular disease?

With regard to the main theoretical model driving the work in this thesis, some important conclusions can now be drawn about the processes involved in the relationship between CVD and MDD and anxiety disorders (summarized in **Figure 1**). First, results of this thesis show that, although dysregulation of the ANS may still play an important role in this relationship, it appears not to be affected by depression and anxiety disorders themselves, but rather by the antidepressant treatment often prescribed in these disorders. However, MDD and anxiety disorders may be related to CVD by autonomic dysfunction in another way than through antidepressant use. For instance, this thesis supports the idea that depressed and anxious subjects exhibit more unfavourable lifestyle habits. As can be observed from the first tables of Chapters 2, 3, 5 and 6, depressed and anxious subjects smoked more (often), had higher BMI, and performed less physical activity than persons without these disorders do. These lifestyle factors have major impact on ANS measures since associations significantly decreased when analyses were adjusted for lifestyle factors and significant associations were found between

ANS measures and lifestyle factors (Chapter 3). Despite the decrease in strength of the associations, the effects remained highly significant (Chapter 2, 3, and 6). The

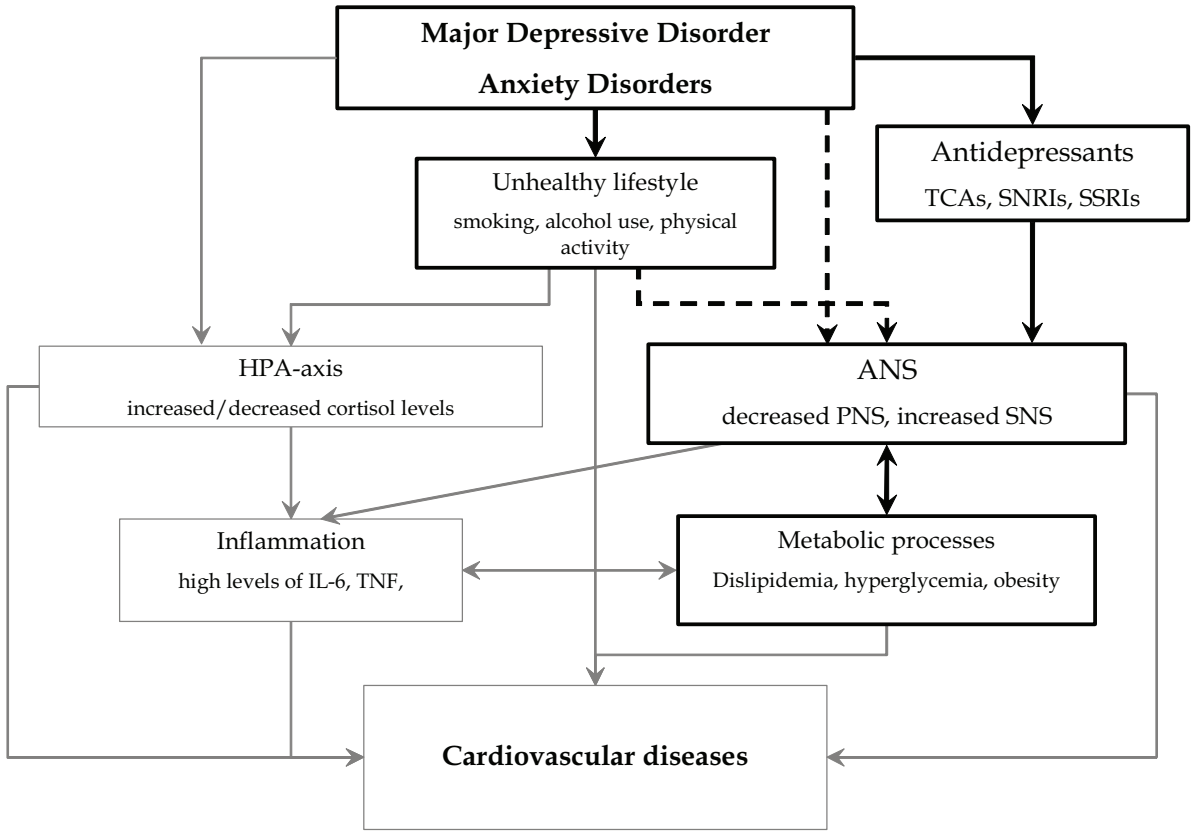

Figure 1. *Schematic representation of possible processes involved in the relation between MDD/anxiety disorders and CVD. Bold lines and boxes point to relation addressed in this thesis*

unhealthy lifestyle seen in depression and anxiety therefore does not explain the relation between these disorders and CVD, but may indirectly contribute to the risk for CVD by influencing cardiac autonomic activity. In addition, the unhealthy lifestyle may influence metabolic processes such as cholesterol and glucose concentrations, which are risk factors for (atherosclerotic) CVD as well[71-73]. Chronic or acute activation of the ANS and HPA-axis is thought to negatively influence metabolic processes and cause an unfavourable metabolic pattern, although the reversed direction of causation may also be in play[67,74]. Disturbed metabolic processes and the metabolic syndrome have been associated with depression and anxiety[58-62]. A separate PhD-thesis (Vreeburg, SA) focussing on the relation between depressive and anxiety disorders and HPA-axis activity, shows that HPA-axis is not or very weakly associated with depression and anxiety. In addition, no relation between the HPA-axis and metabolic or autonomic

dysregulations are found (Chapter 7), whereas ANS activity was highly associated with all kinds of metabolic abnormalities. As yet, no judgement can be given on the direction of this association, since our results are based on cross-sectional analyses. Other studies however, suggest that increased SNS activity influences among others the liver, adipose tissue, kidneys and arterioles, and these organs affect for example lipolysis, insulin production and glucose uptake[44,75-81]. Diminished PNS activity is sometimes described as a consequence of metabolic dysregulations[80,82], but it has also been reported to be a modulator of metabolic dysregulations[66,77,83-89].

Inflammatory processes may also be involved in the relation between depressive and anxiety disorders and CVD. Depression and anxiety have been reported to be associated with increased levels of inflammatory markers such as the cytokines interleukin-6 (IL-6) and C-reactive protein (CRP)[90-100], although the actual contribution to the risk for CVD is questioned[101,102]. Research has demonstrated that inflammation is under control of the central nervous system and increased SNS and diminished PNS activity have been associated with increased cytokine production[77,103-105]. In addition, there seems to be a bi-directional influence of metabolic dysregulations and inflammation in depression. Therefore, it remains unclear whether inflammation characteristics are a direct cause of the psychopathological state or induced by other factors (as well).

In sum, lifestyle factors, metabolic and inflammatory processes, and antidepressant effects on ANS functioning all seem to be involved in the aetiology of CVD and are associated with depression and anxiety disorders as well. These factors may each contribute separately or in combination to the relatively high occurrence of cardiac and coronary diseases in psychiatric disorders.

Methodological considerations

Possible limitations of the present study already have been addressed in the different chapters, but there are several additional general points that need further reflection.

A first point to make is that our longitudinal results are of an observational nature, in contrast to results obtained in a randomized controlled trial of antidepressant use. Despite the fact that a pseudo-experimental setup was created (since persons who became depressed or anxious or started the use of antidepressants served as their own controls) and important covariates were considered, the observational character of the study does not allow a definitive statement on causality. Furthermore, even if the effects on RSA and heart rate are

causal, we cannot be sure that they translate to a higher risk for the development of CVD. NESDA is a reasonably young cohort in terms of CVD risk (mean age 42 years) and only 2-year follow-up data was available. Therefore, it could not be meaningfully examined whether persons using antidepressants and showing an unfavourable autonomic profile actually display cardiovascular diseases more often and sooner than persons with a normal cardiac autonomic profile do.

As has been suggested in Chapter 6 and in the section on SNS activity in anxiety disorders in Chapter 8, individual differences in sympathetic control, using the PEP, may have been confounded by individual differences in preload and afterload. To deal with afterload, the mean arterial pressure (MAP) was used, but this is an imperfect proxy for aortic pressure. The influences of preload on PEP still is a matter of debate[30-32], and no valid correction factor is described to date[106]. This could mean that the difference in average PEP that was found between groups may have been influenced by differences in preload. Another issue that concerns PEP is the fact that no longitudinal data was available at the time that these studies were conducted. Therefore, it was not possible to provide additional evidence that the dysregulated SNS seen in persons on antidepressants was actually caused by these antidepressants, as could be done for vagal tone and heart rate.

Possible effects of severity of MDD or anxiety are a further point of concern. Depressed and anxious antidepressant users had similar severity scores as currently or severely depressed and anxious non-users did, but had higher scores than antidepressant- naïve persons with mild severity or a depression or anxiety disorder in remission (Chapter 2 and 6). Although adjustment for severity did not change any of the results (Chapter 2 and 3), it is likely (and desirable) that severity was decreased by the use of antidepressants. Thus, it could be that persons on antidepressants had higher values of symptom scores and were more severely ill before the start of antidepressant treatment. Subsequently, it could be hypothesized that the observed cardiac autonomic effects of antidepressants actually reflect effects of severity. However, if the true effect would lay in the disorder itself, in this case in the severity of the disorder, at least some effects of being depressed or anxious should have been observed in the longitudinal analyses on ANS measures, but none were found. A last consideration is the fact that some persons on TCAs might have been non-responders to treatment with SSRIs or SNRIs and may represent a group with severe psychopathology that is difficult to treat and study.

Future studies

The topics discussed in the previous paragraph on considerations already suggest some directions for future research. A summary of possible relationships and associations of interest for future investigations, with regard to the focus of this thesis and considering the presented results, is given in **Figure 2**. An apparent future step would be to follow the participants over longer periods of time in order to (a) map the course of antidepressant use and ANS functioning (especially SNS control, since longitudinal studies on this subject are missing).

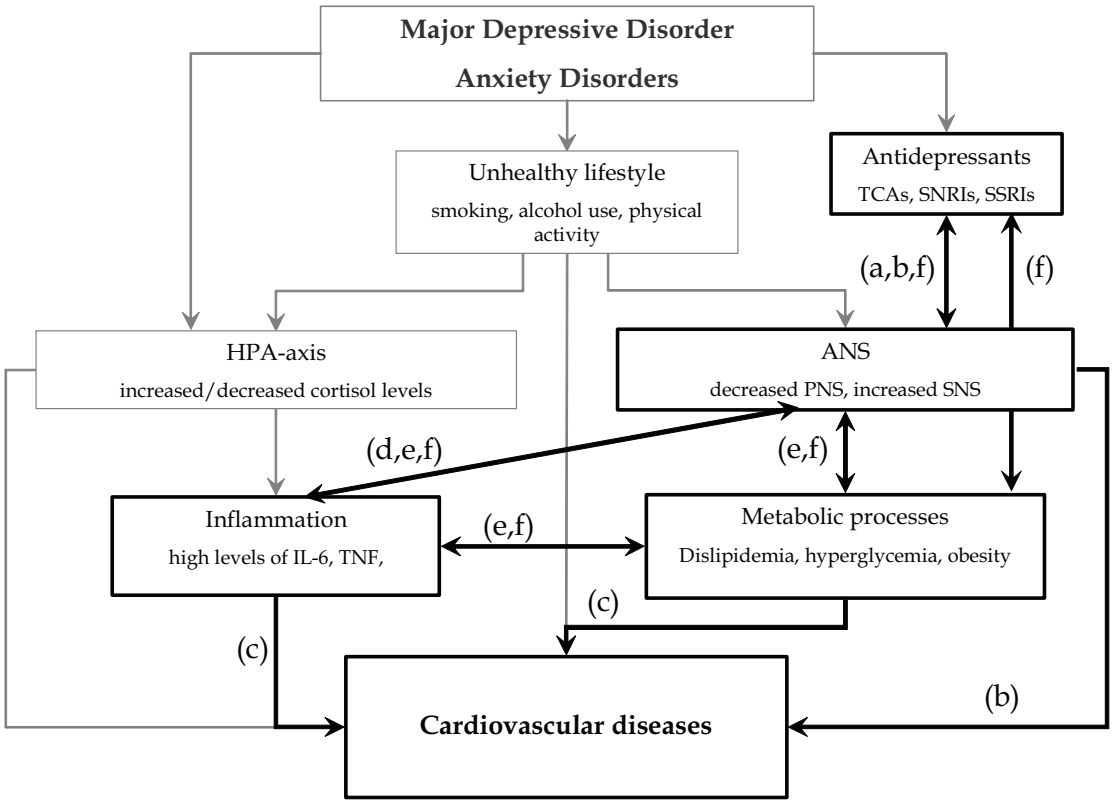

Figure 2. *Relations between depression and anxiety, inflammation, metabolic processes, HPA-axis, ANS and cardiovascular diseases. Bold arrows indicate suggestion for possible future research*

In addition, (b) the occurrence of CVD can be compared between persons who are using and persons who are not using antidepressants to confirm whether the relationship between antidepressant use and ANS activity truly is a risk factor for CVD, and (c) the predictive value of metabolic and inflammatory processes for the risk of CVD can be investigated as well. Because of the relatively young cohort of NESDA and the short follow-up period that has been achieved to date, another option to answer this question would be to study an older population with higher prevalences of CVD. Studies in an older population of depressed (like the

Netherlands Study of Depression in Older people, NESDO) would additionally make it possible to investigate the effects of late onset of depression, which is linked to several biological processes such as atherosclerosis[107,108].

The relationship between ANS functioning and inflammatory markers needs more clarification (d) and can be studied in the large NESDA cohort, cross-sectionally as well as longitudinally. In addition, (e) longitudinal examination of the tripartite relationship between ANS activity, inflammation and metabolic dysregulations may provide information on the direction of these relationships and possible interactions between these systems. Introducing antidepressant use in this triangle (f) enables us to uncover whether the interrelationships are driven by the effects of antidepressants (on ANS functioning).

Besides the possible studies depicted in Figure 2, several other investigations are worth performing. It is suggested that ANS functioning and reactivity might be indicators of responsiveness to antidepressant treatment[101,102]. In addition, inflammatory markers have been found to relate to antidepressant use and may respond to or predict treatment resistance as well[77,103-105]. This implies that there could be a subgroup of subjects using antidepressants that exhibit a particularly poor autonomic or inflammatory profile and specifically these subjects may not improve from antidepressant therapy. Since a considerable number of persons treated with antidepressants do not benefit from this therapy (are resistant) it would be very useful for clinical practice to study possible predictors for treatment response. The large sample size and prospective character of NESDA would enable us to investigate the possible predictive values of ANS functioning and the role of other biological pathways such as HPA-axis functioning and metabolic processes. Experimental designs that measure inflammation, autonomic function, and severity of depression or anxiety before and after treatment with antidepressants can determine whether improvement by antidepressants is accompanied by changes in autonomic or inflammatory profile.

Future research should also address autonomic stress-reactivity. It is suggested that some relations between mental problems and autonomic function do only show under acute stress[109,110]. By exposing participants to a stressor (such as a stressful computer task or cold pressor test) and measuring autonomic function before and after administration of this stressor, the autonomic reactivity or response can be measured. In this thesis, no differences were found in basal autonomic levels between MDD/anxiety and healthy controls, however since no substantial stress was induced any depression or anxiety-related effects that

appear only during acute stress might have been overlooked.

Finally, autonomic dysfunction has been linked to prefrontal brain areas and nuclei in the brain stem[111-114]. It would be interesting to examine whether the dysregulated autonomic function, specifically that seen in antidepressant users, is also linked to altered activity in these brain areas. Functional magnetic resonance imaging (fMRI) was performed in a subset of the NESDA population, and enables us to associate these images with ANS indicators to answer this question in the near future.

Clinical implications

This thesis provides results that are of importance for clinical practice, not only for psychiatry, but also for cardiology and general practice. Because of the relatively high comorbidity of depression and anxiety disorders and CVD, psychiatrists and cardiologists will often see patients with both disorders and should be aware of the effects of antidepressants on autonomic function. In addition, general practitioners (GPs) should be aware of these unfavourable effects of antidepressants as well. Not only do they see so many people because of their specific role as a social safety-net and advisor, but also because the prescription of antidepressant by general practitioners has witnessed a major increase in the past ten years (it is thought that 80% of the antidepressants is now prescribed by GPs[115]). Other possible kinds of therapy could be considered and if the severity of the disorder obliges antidepressant treatment, an antidepressant with the least unfavourable (side)effects should be prescribed. When, nonetheless, a TCA or SNRI has to be prescribed, it should be advised to monitor these patients carefully to detect changes in cardiac health as soon as possible. This holds for all psychiatric patients of course, but especially for those who already suffer from CVD or display risk factors for getting CVD, such as high blood pressure, high cholesterol, or familial vulnerability. In addition, patients who have had several recurrent depressive or anxious episodes seem to have a poor prognosis and are often advised to stay on antidepressants to prevent the development of new episodes (as a kind of prophylaxis). This group of patients also deserves special attention because the long duration of antidepressant use and autonomic dysregulation could specifically increase the risk for CVD. This being said, an important question needs to be considered: Does the dysregulation of autonomic function and the possible (but not indisputable) risk for CVD outweigh the beneficial effects of antidepressant medication on mental health and future (heart) disease? In view of

the large number of patients comorbid for depression and (heart) disease, this is an important question that needs to be addressed.

Overall conclusion

This thesis shows that there is no relationship between depression or anxiety disorders and vagal control and cardiac sympathetic control. However, it appears that antidepressants have an unfavourable effect on autonomic activity. All antidepressants were related to decreased cardiac vagal control and use of TCAs or SNRIs seemed to increase heart rate and cardiac sympathetic control, whereas SSRIs decreased heart rate and sympathetic control. This implicates that the hypothesized role of ANS functioning in the relationship between depressive and anxiety disorders and CVD might still exist, but that it operates mainly through the effects of antidepressant use rather than through depression/anxiety itself. These findings may have important consequences for clinical practice, especially for the anxiety or depression patients with an unfavourable CVD risk profile.

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