Chapter 8

Summary & general discussion

8.1 Introduction

The present thesis examined the association between depression and risk factors for cardiovascular disease, smoking, cortisol, and blood pressure in a large population sample ascertained from the Netherlands Twin Register (NTR). Depression was measured in two ways: 1) as an anxious depression factor score based on longitudinal survey data, and 2) as incidence of life-time clinical depression based on a psychiatric diagnostic interview. Smoking was assessed by means of survey data in 4584 participants. During a representative day salivary cortisol samples and ambulatory blood pressure measurements were obtained in 431 persons. This chapter discusses the results for each measured parameter and attempts to formulate a general conclusion from the results of the preceding chapters. In conclusion some recommendations for future research will be made.

8.2 Validity of the anxious depression score

An anxious depression factor score was computed for the purpose of identification of the genes involved in anxiety and depression in future. This score was based on the multivariate analysis of anxiety, neuroticism, and depression in twins and their siblings and represents the genetic vulnerability to anxious depression. The analyses in the current thesis were based on this score. To ensure that the anxious depression factor score indeed represented vulnerability to anxiety and depression, the anxious depression factor score was validated against a clinical measure of depression obtained from the Composite International Diagnostic Interview (CIDI). Validation of anxious depression against DSM-IV depression in the sample that participated in the 1997 survey is presented in Chapter 3. Findings confirmed that the anxious depression factor score reflected the vulnerability to clinical depression. A strong association between the anxious depression factor score and the categories of the DSM-IV diagnosis for depression was found. In general it appeared that high anxious depression was associated with high risk of a DSM-IV depression diagnosis. Especially the diagnosis of recurrent depression and severe depression was more prevalent in the persons with high factor scores.

Based on the results of the validation study it can be concluded that the composite factor score, combining both anxiety and depression scales, indeed represents the vulnerability to clinical depression and can be used as a reliable measure of trait depression.

8.3 Smoking status

In Chapter 4 the association between smoking and depression was assessed in a family based population. The assessment of smoking status was based on both longitudinal survey data and on interview data obtained on the measurement day. Smoking status derived from this data categorised the participants into three groups: non-smokers, ex-smokers and current smokers. First the association between smoking and depression was assessed in the whole sample and in addition to control for possible common aetiologic factors underlying the association, in a between family and within family design. In the whole sample, both men and women that had either a high score on anxious depression or a clinical depression were more often smokers than non-depressed persons. The association between depression and smoking appeared to be extra strong in the youngest age cohort (15 to 25 years). Since smoking initiation occurs in this age cohort, it is possible that depression is a mediating factor in smoking initiation. Women who were diagnosed with DSM-IV depression appeared to be more often current smokers and less often ex-smokers than men diagnosed with DSM-IV depression. This supports the suggestion that women, more than men use smoking as a means to reduce depressive symptoms and are therefore less able to cease smoking. Non-depressed persons from families with a positive family history were also more likely to be current smokers or ex-smokers compared to non-depressed persons from families with a negative family history for depression. Even though these persons had themselves a higher mean anxious depression score than persons from a negative family history, this could indicate that having a positive family history for depression increases vulnerability to smoking initiation. In sum, smoking status proved to be strongly associated with both anxious depression and clinical depression, particularly in the youngest cohort in the study. Therefore, smoking is a likely mediating factor in the association between depression and cardiovascular risk.

Apart from a strong association between smoking and depression, smoking was also found to be associated with both cortisol and ambulatory blood pressure levels. The stimulating effects of smoking on both cortisol (Wilkins et al., 1982; Pomerleau and Pomerleau, 1990; Kirschbaum et al., 1992; Del Arbol et al., 2000) and blood pressure (e.g. Oncken et al., 2001; Kannel & Higgins, 1990; Sleight, 1993; Kochar & Bindra, 1996) were also found in this thesis. More specific, in the assessment of cortisol levels in Chapter 6 it appeared that current smokers had higher cortisol levels during the day, i.e. on the second morning sample and the afternoon sample, but lower cortisol levels at awakening. Furthermore, in the assessment of ambulatory blood pressure (Chapter 7) levels it was found that smokers and ex-smokers had higher blood pressure than non-smokers. It is therefore surprising that smoking status was not always considered as a major confounder in earlier studies that assessed the association between depression and cortisol and depression and blood pressure.

8.4 Cortisol

In the current thesis, no association between daytime cortisol levels and depression, both trait and clinical, was found. Noteworthy is that there are only a few studies with a similar sample size as reported on in the current thesis (n=338). Only the studies by Brandtstadter et al. (1991, n=767), Strickland et al. (2002, n=343) and Mazur et al. (1994, n=4462) provided data on larger samples and found no association between depression and cortisol levels.

A major strength of the design used in Chapter 6 was the availability of both trait levels of anxious depression, which reflect an individual's vulnerability to clinical depression and clinical depression. In addition to the assessment of an association between depression and cortisol levels in the whole sample, a similar assessment within and between families was performed. This way aetiologic mechanisms related to familial factors could be accounted for. Most of the earlier studies reviewed in Chapter 6 reported cortisol levels of in-patient samples that had a history of major depression, or they reported trait depression derived from personality questionnaires administered on the measurement day. But none of the studies reviewed in Table 1.1 in Chapter 1 of this thesis provided such a complete assessment of both trait and clinical depression as in the present thesis. Furthermore, based on the strong association found in the literature between smoking and cortisol levels and smoking and depression special attention was given to the confounding role of smoking. It was rather remarkable that only a few studies from the review in Table 1.1 mentioned cigarette smoking as a confounder.

Cortisol was measured in saliva. This method is relatively new to the field of cortisol studies (Bartels et al., in press). It was decided mainly because saliva collection is, as opposed to collection of blood samples, not an invasive method and therefore not a stressor. Furthermore, it is easy to perform by the participants themselves, and therefore does not require professionals to handle needles. Finally saliva cortisol sampling can be done in any setting and is therefore ideal for ambulatory measurements. From the results in Chapter 6 it is clear that saliva sampling provides the expected circadian variance in the cortisol profile. The participants in the study had no trouble to comply with the cortisol sampling protocol during their daily activities, illustrating that this strategy is useful for cortisol sampling in large populations.

However, no association between depression and cortisol was found in the current study despite the large sample size, control for possible confounders and valid assessment of cortisol and trait and clinical depression.

8.5 Blood pressure

In Chapter 7 the association between depression and blood pressure was assessed. Analysis on trait levels of anxious depression revealed no significant association between depression and high blood pressure. The association between life-time depression and ambulatory blood pressure, however, appeared to be significant. Both diastolic blood pressure and systolic blood pressure

levels were higher in persons who had experienced a life-time clinical depression compared to persons who never had experienced such an episode. When the confounding influences of posture/physical activity on the day of measurement and of age, sex, BMI, smoking and medication status were taken into account, clinical depression was still associated with higher systolic blood pressure, but the association was found to be most pronounced in older women.

Our findings confirm findings of previous studies on the positive association between depression and ambulatory blood pressure. However, compared to other studies our study adds to the literature on two important points. 1) In this study a major advantage was the assessment of both trait depression and clinical depression. The results showed that not the vulnerability for developing a clinical depression is associated with higher blood pressure levels but only having experienced a clinical depression itself. 2) In this study possible influencing factors on which depressed persons differ from non-depressed were strictly controlled for. Because depressed persons have repeatedly been found to be less physical active during the day, controlling for posture and activity effects on blood pressure during the measurement day is appropriate in an ambulatory measurement design. Therefore, only blood pressure registrations obtained during sitting postures were included in the final analyses in Chapter 7. Second, since both depression and blood pressure are know to be associated with smoking status, age, sex, BMI and medication use, these confounders were taken into account in the current study as well. Inclusion of confounders in the analyses in fact revealed that the effects of clinical depression on ambulatory blood pressure were not as straight forward as had been reported before in previous studies. Unfortunately inclusion of all these confounders also meant that the within and between family design as used in chapter 4 (smoking) and 6 (cortisol) could not be performed on the blood pressure data: even though the number of participants in ambulatory monitoring was quit large, within or between family analyses required more families when controlling for so many confounders is necessary.

In sum, this largest ambulatory blood pressure monitoring study to date has confirmed the existence of a significant association between blood pressure and depression. This relation, however, was not as straight forward as reported in previous studies. A diagnosis of life time depression, but not a high anxious depression score, was associated with elevated blood pressure. This association was attenuated by controlling for smoking and BMI, and modulated by age and sex.

8.6 Synthesis

In the present thesis, an a priori decision was made to measure possible risk of cardiovascular disease in depression in a normotensive, non-clinical population. Although life-time clinical depression was determined, there was no division in acute or remitted depression. The rationale for this approach was that if according to the stress diathesis model of depression, depression was associated with biological alterations, these would also be present in remitted depression and to a

lesser extent in persons at risk for a clinical depression who had not already experienced a depressive episode. Participants were ascertained from Dutch twin families. Because twinning occurs in each region and at all socio-economic levels, ascertainment through a twin register yields a representative sample of the population at large. It is therefore assumed that the results from the present thesis can be generalised to the population at large.

In the present thesis depression was associated with a number of health risk factors. Persons with a DSM-IV diagnosis for depression differed from non-depressed persons in that they had higher BMI and were more often current or ex-smokers. Persons with a DSM-IV depression were in general older than persons who were not diagnosed with depression and possibly in relation to that DSM-IV depression was associated with more medication use in general. High anxious depressed persons, who were at risk for a clinical depression, were more often current or ex-smokers than low anxious depressed persons. From the results on the health risk behaviours it can be concluded that clinical depression is associated with an unfavourable risk profile for cardiovascular disease.

The results from the analysis on depression and salivary cortisol and depression and ambulatory blood pressure were less unambiguous. The hypothesis was that there would be increased sympathetic and reduced parasympathetic drive in depressed persons which would in time result in elevated cortisol and blood pressure levels. No evidence of higher cortisol levels was found for either anxious depression or clinical depression. This does not mean, however, that there is no disturbance on the CNS-CRF pathway, since cortisol is an end product of a chain of events regulated by various feedback mechanisms. One important reason why the present study did not find the association between depression and cortisol could be that cortisol was measured in a population sample. Other population sample studies did not find the expected relationship (e.g. Brandtstadter et al., 1991; Mazur et al, 1994; Strickland et al, 2002). It could be that a clinical diagnosis of depression is required for elevated cortisol levels. However, no association was found between depression and cortisol levels in DSM-IV depression either. An alternative explanation for the lack of evidence for an association between depression and cortisol is that it is only found in acute depression as opposed to remitted depression. Support for this possibility is found in a study by Trestman et al. (1995). The explanation for higher cortisol levels in acute depression is that experiencing depression or even hospitalization may be a stressor in itself that causes chronic stress-reactivity resulting in high cortisol levels (Maes et al., 1994). Results from the blood pressure analyses showed no effects on anxious depression but elevated blood pressure in clinical depression. After controlling for the relevant confounders, age, sex, BMI, smoking, the effect appeared to be attenuated and significant only for systolic blood pressure in older women, and -to a lesser degree- in younger women and in men.

Since elevated blood pressure can be seen as the end product of autonomic deregulation it is possible that this is the underlying mechanism explaining the elevated blood pressure levels in this study. Depression has been associated with sympathetic overactivation (Dawson, Schell &

Catania, 1977; Iacono et al. 1983; Ward, Doerr & Storrie, 1983)and reduced parasympathetic activity (Carney et al., 1995; Krittayaphong et al., 1997; Watkins & Grossman, 1999). Autonomic deregulation may account for the higher systolic blood pressure levels found in older women who were diagnosed with DSM-IV depression. To reliably answer this question it is necessary to have recordings of heart rate, impedance cardiogram and respiration. From these two variables two reliable measures of sympathetic and vagal tone can be derived, namely: pre-ejection period (PEP), respiratory sinus arrhythmia (RSA) and the root mean square of the successive differences (rMSSD). Recordings of heart rate and respiration were made and these data will become available in the near future.

8.7 Future research

This study is the first in a large project in which it is attempted to identify the genes that are involved in anxiety and depression. Furthermore the goal of the project is also to identify endophenotypes, or biological markers of anxiety and depression, which can enhance the knowledge on the mechanisms underlying anxiety and depression. The follow-up on the ambulatory measurement started one year ago and will yield a larger sample of twins and siblings and consequently more complete families. Also more complete monozygotic and dizygotic twin pairs will be included. The benefit of more complete families and more complete twin pairs is that it will from now on be possible to include genetic analysis into the research design. This will reveal more information on the possibility that there are common genetic factors underlying the association between depression and cardiovascular disease risk.

Finally an interesting point in the within family analysis has to be made with regard to the unaffected sibling of the discordant sib pair. It is often assumed in within family analyses in which a trait (e.g. smoking) is compared between the index sib and the unaffected control sib that any resemblance between the siblings would reflect familial factors not related to depression. However, as found in Chapter 4 the non-depressed siblings from families with a positive family history for depression had more often a high anxious depression score than the non-depressed siblings from the families with a negative family history for depression. Moreover it must not be forgotten that the unaffected siblings of families with a positive history of depression experienced a negative life event when one of their siblings experienced a clinical depression. This fact alone can put high stress on a family. It is therefore recommended that for further within family analysis not a first degree unaffected relative is compared to the index sibling, but a second degree unaffected relative, i.e. a cousin.