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Depression and Risk of Cardiovascular Disease in older General Practice patients
Considering the enormous burden and costs of cardiovascular diseases (CVD), especially among older persons. CVD is worldwide the leading cause of death and knowledge of any amenable risk factor is of importance. Depression is thought to be such risk factor: there is a high prevalence in all medical settings (including the general practice), it is eminently treatable, and it may raise the subsequent risk of CVD events and mortality three to five fold for patients with a history of CVD. Although most literature will favour a yes on the question: “Is depression an independent risk factor for CVD events?” there is a great amount of variation across studies (Chapter 2). Little is known whether depression actually raises CVD risk in a sample of elderly patients seeking care in Dutch general practice, and even less is known about potential mechanisms that may link depression to CVD.

In the present thesis we had two main research questions:
• Is depression a risk factor for the development of CVD in Dutch elderly general practice patients?
• Exploration of pathways through which depression may be linked to CVD
  a. Does depression contributes directly to the pathophysiology of CVD?
  b. Does depression affects health-related behaviour, which in turn influences the risk of CVD?

Literature review (Chapter 2)
A systematic review of the literature was done on whether depressed patients or people with depressive symptoms have an increased risk of cardiovascular diseases. Although previous literature reviews reported that depression is an independent risk factor for the onset of coronary heart disease, it is not clear to what extent depression is associated with the onset of other diseases of the circulatory system. In our systematic review we aimed to estimate the risk of depression as an independent risk factor for various cardiovascular diseases (CVD) and explored the effects of variation across studies (heterogeneity) and methodological quality. In the electronic databases MEDLINE and PSYCHINFO we searched for longitudinal cohort and case-control studies reporting depression at baseline and CVD outcomes at follow-up. We measured the methodological quality and used meta-analyses analyses to calculate an overall risk factor and the influence of heterogeneity.

Of the 28 studies that met the inclusion criteria, 11 were assessed as high quality studies. Although depressed mood increased the risk for a wide range of CVDs, heterogeneity was substantial in most cases. Only the combined risk for the onset of myocardial infarctions found in eight studies was homogenous and showed
a 60% increase. When looking at individual methodological components of all studies it showed that clinically diagnosed major depressive disorder (MDD) was the most important risk factor for developing CVD. Unfortunately clinical diagnosed MDD was only measured in 4 studies. Therefore, given the variation between studies, there are still doubts about the robustness of depression being an independent risk factor for the onset of CVD.

**Depression in the Dutch General Practice (Chapter 3)**

There is little knowledge about the prevalence of depression in older patients consulting their general practitioner. In this chapter we estimated the prevalence of major and minor depression in Dutch older GP attendees. Our estimation was based on a cross sectional screening for depression in 17 urban and 41 rural General Practices. The screening was conducted in two stages.

The first stage used the Geriatric Depression Scale-15 items (GDS-15) as a screening instrument for depression, which was send by mail. Of all GP attendees of 55 years and older, 5668 persons returned their GDS-15 meaning a response of 62%. In stage two all GP attendees with a GDS-15 score of 5 or higher, were subjected to a diagnostic interview using the Primary Care Evaluation of Mental Disorders (PRIME-MD). To estimate the proportion of false negatives, a random sample of 100 GP attendees with GDS-15 scores below five were interviewed as well.

The prevalence of major depression among GP attendees was 13.7% and for minor depression 10.2%. GP attendees with major depression were on average almost 2 year younger and more often female when compared to those with a minor or no with depressive disorder. GP attendees with major depression lived more often in urban districts. Only 22% were treated with antidepressants. We conclude that depression in older GP attendees is a very common health problem and it is important to identify untreated patients with a high risk of persistence of depression. This could help to focus the limited resources available in general practice to those patients in whom treatment is most urgently needed.

**Our depression study**

The main findings of this thesis, described in chapter 4 to 7, are based on a cohort of 143 depressed and 139 non-depressed (age- and gender-matched) controls of 55 years and older GP waiting-room patients with a follow-up period of two years. Depression was diagnosed during a diagnostic interview according to the fourth edition of the Diagnostic and Statistical Manual of mental disorders of the American Psychiatric Association (DSM-IV) criteria for Major Depressive Disorder using the PRIME-MD. Cardiovascular risk factors and potential confounding factors were measured in a baseline examination. Depression severity and lifestyle measures (smoking, drinking
alcohol and physical activity) were assessed with validated assessments at baseline, six, twelve and twenty-four months. During the follow-up period information was collected on physical health, depression status and behavioural risk factors. Cardiovascular disease end-points were identified with annual questionnaires and cross-checked with the general practitioners medical records.

**Baseline characteristics (Chapter 4)**

This chapter presents the baseline characteristics of our cohort and analyses the differences between the older depressed patients and the non-depressed control group. Recent studies have suggested that the association between depression and cardiovascular disease may include both physiological and behavioral mechanisms. We examined whether depressed older general practice patients were over exposed to behavioral or physiological risk factors for cardiovascular disease, and, if so, whether these are modified by common risk variables such as; age, gender, functional disability and existing cardiovascular disease.

Compared to the non-depressed controls, the depressed patients in our study had a decreased heart rate variability (see Chapter 5), and were less physically active. The reduced physical activity in depressed patients was reinforced by older age and functional disability. Depressed women had a tendency to be more obese. Remarkably, existing cardiovascular diseases did not modify the association between depression and the risk factors.

In general, older depressed general practice patients are equally exposed to most physiological and behavioral risk factors of CVD. Only in selected subgroups such as the oldest patients and those with functional disabilities, some risk factors were more pronounced. This supports the notion that adequate management of late life depressive disorder should include a thorough assessment and, if appropriate treatment of co-existing cardiovascular risk factors.

**Heart rate variability (Chapter 5)**

Chapter 5 is a more detailed description of the baseline characteristics of our cohort. It focuses on the heart rate variability (HRV) measures. HRV measures are indicators of the autonomic nervous system. The objective of this chapter was to determine whether older general practice patients with a Major Depressive Disorder (MDD) have lower HRV compared to non-depressed patients.

HRV was measured with an electrocardiogram (ECG) during a 5-minute supine rest. The results showed two statistically significant differences between the depressed patients and controls. The Standard Deviation of all NN intervals, which is seen as an estimate of overall HRV, and the mean difference in HF-power reflecting the respiratory sinus rhythm were both lower for the depressed patients. These differences
in HRV may help explain why depression is a risk factor for cardiovascular disease and mortality.

The longitudinal relationship between depression and life-style measures (Chapter 6)
One of our research hypotheses stated that depression affects health-related behaviour (life style), which in turn influence the risk of CVD. In this chapter we investigated if major depression and negative life-style behaviour are related over time and show a synchrony of change.

Depression severity and lifestyle measures (smoking, drinking alcohol and physical activity) were assessed with validated assessments at baseline, six, twelve and twenty-four months. Although depressed patients did not differ over time from the control group in negative life-style behaviours as smoking and drinking, they had a lower level of physical activity. Nevertheless there was no clear evidence for a synchrony of change between depression and physical activity. High baseline physical activity was a remarkably good predictor for depression recovery; therefore promoting physical activity in depressed patients with low physical activity may improve depression outcomes.

Incidence of cardiovascular diseases (Chapter 7)
Community-based studies reported that depression is an independent predictor for the onset of clinical cardiovascular disease. However, there is very little data available on older depressed general practice patients. Chapter 7 reports on the incidence of cardiovascular diseases during the two-year follow-up period and investigates if major depression in older general practice patients was an independent risk factor for incident cardiovascular events.

The incident CVD events were collected by an annual questionnaire. For confirmation, incident cases and missings were crosschecked with the general practitioners medical record. In our cohort, twenty-eight participants experienced a cardiovascular event during the follow-up period of 2-year. CVD events were more frequent among the depressed patients. Even after adjusting for common confounding variables depressed patients had a 2.5 times higher risk on a CVD event.

General Discussion (Chapter 8)
The general discussion summarizes the findings on our main research questions described in this thesis. First, is depression a risk factor for the development of CVD in Dutch elderly general practice patients? During the two-year follow-up of our study twenty-eight participants experienced a cardiovascular event. Major depression was associated with an increased hazard ratio of 2.5 (95% confidence interval, 1.02-5.9)
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for cardiovascular events, controlling for gender, smoking, and history of cardiovascular disease.

Second, when exploring pathways through which depression may be linked to CVD we found that there were no relevant differences in Framingham index at baseline (depressed: 17.62 SD 11.40; controls 17.30 SD 11.72; 95% confidence interval 0.98 (0.95, 1.02)). Prior cardiovascular disease did not increase the cardiovascular risk index in depressed patients. Nevertheless, depressed patients had decreased heart rate variability. Functionally disabled depressed patients had a prolonged QTc interval on the electrocardiogram. On the question, whether depression affects health-related behaviour, which in turn influences the risk of CVD, depressed patients were less physically active. We were not able to demonstrate a synchrony of change between depression and life-style measures. Depression recovery was only associated with a higher baseline level of physical activity.

Furthermore methodological discusses and conceptual aspects when researching the connection between a mental disorder and diseases are discussed. Finally, we discuss the clinical implications of the results presented in this thesis on the daily practice of GPs and we make suggestions for further research.

Reasons for non-response (Appendix 1)

Depression screening can improve identification and subsequent treatment of depression in general practice. In this appendix we assess the response of elderly Turkish and Moroccan general practice patients on a postal depression screening using the GDS-15 and trace reasons for non-response.

Compared to the response rate of Dutch elderly (n=6060, 61.7%) the response of Turks (n= 39, 30.7%) and Moroccans (n=119, 31.1%) elderly was signifi cant lower. Most important reason for non-response among Turkish elderly was “temporary other place of staying” (Turkey). Among Moroccans it was “illiteracy”. The low response rate and reasons for non-response implicate that other means to approach migrants’ sub-populations should be sought.