Somatic depression in the picture

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Chapter 7

General discussion

The overall aim of this dissertation was to contribute to a better understanding of the association between depression and somatic disease. For this purpose several potential pathways explaining this association were examined, including psychological, biological, and behavioral pathways (Figure 1). Furthermore, the role of confounding by prognostic factors was examined, to take the possibility of a non-causal pathway into account. The somatic diseases that were addressed in this dissertation were hypertension, diabetes, chronic kidney disease (CKD), and coronary artery disease (CAD). Below the findings are interpreted and integrated. Also, methodological considerations, directions for further research, and clinical implications are discussed.

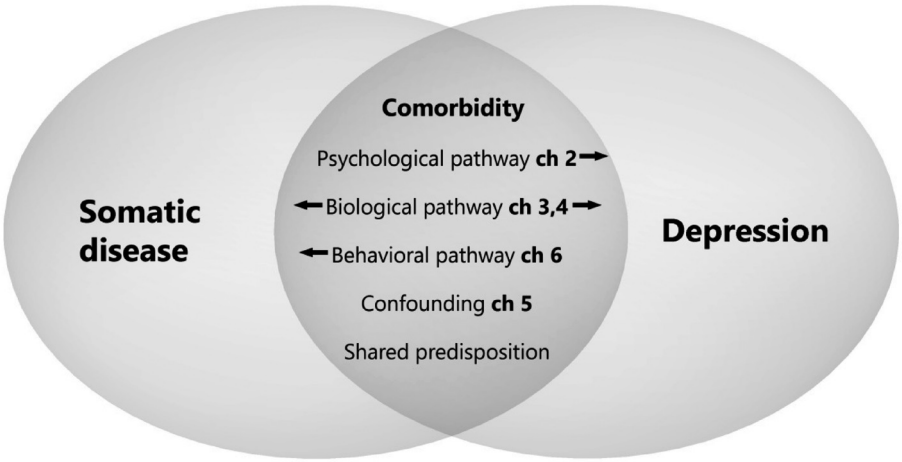


Figure 1: Overview of potential pathways leading to the comorbidity of somatic disease and depression

Summary and interpretation of the results

Psychological pathway: psychopathology in diagnosed and undiagnosed diabetes
In ***Chapter 2*** we found that in a large cohort of more than 90,000 participants, the odds of depression for individuals with diagnosed and undiagnosed diabetes (individuals unaware of having diabetes) were equally increased, compared to individuals without diabetes. In contrast, odds of anxiety were only increased in individuals with diagnosed diabetes. This was after adjusting for potential confounders that could explain the difference in psychopathology between diagnosed and undiagnosed diabetes, including co-morbid anxiety, depression and diabetes severity markers.[1-4]

Because odds of depression were equally increased for diagnosed and undiagnosed diabetes, the *psychological* consequences of having a diabetes-

diagnosis were unlikely to account for this increased depression risk. Instead, a biological factor is likely to underlie the association between depression and diabetes, as individuals who were unaware of their diabetes already had increased odds of depression. In this case, biological processes related to depression may have led to the onset of diabetes, or diabetes-related pathophysiology may have led to the onset of depression, or both. Because odds of anxiety were only increased in diagnosed diabetes, the psychological consequences of the diagnosed diabetes may account for this increased anxiety risk. Thus, distinctive mechanisms may underlie the associations of depression and anxiety with diabetes.

It should be noticed that our findings are in contrast with a large Chinese population-based study[4] and a meta-analysis[5] that found that only diagnosed diabetes was associated with increased depression risk. Differences in depression assessment, (un)adjustment for confounders, and sample sizes may account for these conflicting findings.

Biological pathway: brain structure in early and advanced vascular disease

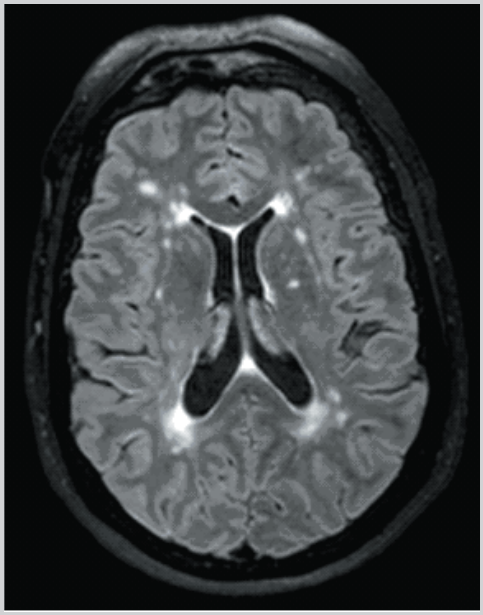
Numerous biological mechanisms have been proposed to underlie the bi-directional association between somatic disease and depression, e.g. inflammation and heart rate variability.[6] Of interest, both depression and vascular diseases have been associated with neurobiological changes, occurring in partly overlapping brain regions.[7-9] Neurobiological abnormalities could possibly predispose to depression and somatic disease, or could be the result of vascular pathology related to the somatic disease, as is suggested by the vascular depression hypothesis,[10,11] or both. Box 1 provides some theoretical background on the vascular depression hypothesis.

In ***Chapter 3*** we reported on the observation that major depressive disorder (MDD) and hypertension were interactively associated with altered gray matter volumes. MDD in the presence, but not in the absence of hypertension was associated with lower volumes in areas implicated in the regulation of emotional and autonomic functions; i.e. the anterior and mid cingulate cortex.[7-9] The findings were independent from age, sex, and anxiety disorders.

As we could not infer temporality in this cross-sectional design, multiple pathways might have accounted for the findings. First, pathophysiological consequences of MDD and hypertension might have synergistically led to the observed interaction effect on reduced gray matter. This would be in line with findings that somatic disease and depression were interactively associated with poor medical prognosis.[12] Accordingly, previous research has demonstrated that depression as well as hypertension contributes to regional gray matter volume decline.[7,13] Our findings are also consistent with the concept of vascular depression.[10,11] Nevertheless, the vascular depression pathway seems unlikely in our sample. This is because the sample consisted of individuals in an early or prodromal stage of somatic disease, i.e. mainly newly-detected hypertension in

Box 1: Theoretical basis of the vascular depression hypothesis

The vascular depression hypothesis postulates that vascular pathology may lead to depressive symptoms by affecting (sub)cortical structures involved in mood-regulation, as well as disrupting white matter tracts that connect these structures (i.e. frontal-subcortical networks).[10,11] This hypothesis arose from the observation that depression in older individuals is frequently accompanied by vascular risk factors and structural brain abnormalities on magnetic resonance imaging (MRI). Vascular depression is generally also characterized by a late age of depression onset, no family history of depression, cognitive deficits, disability disproportional to the depression severity, and poor antidepressant-response and depression outcomes.[19,20] The vascular depression hypothesis implicates an important role of atherosclerosis in the origin of depression.[19] Atherosclerotic processes lead to stiffening and narrowing of blood vessels, resulting in a lack of vasomotor reactivity. Consequently, the ability of compensatory auto-regulatory mechanisms to maintain optimal cerebral perfusion is reduced. If perfusion is not sufficient to provide the necessary amount of oxygen and glucose to the brain tissue, this may result in ischemic brain damage. Ischemic damage to the white matter of the brain appears as hyper-intensities on MRI (see figure below). White matter hyper-intensities are commonly observed in individuals with cerebrovascular risk factors (e.g. diabetes, cardiac disease, hypertension, and chronic kidney disease (CKD)), but are to a lesser extent also common during normal aging.[21] In addition, atrophy of gray matter is related to vascular disease and aging.[22,23] Importantly, ischemic injury has been found to be most prominent in the frontal lobes,[24] where networks for the regulation of mood are located.[25,26] Because frontal brain regions are also involved in the regulation of autonomic functions,[8] ischemic damage further exacerbates hemodynamic dysregulation. Consistent with the vascular depression hypothesis, studies in patients with cerebrovascular disease and elderly individuals with cardiovascular (CV) risk factors implicate a prospective association of cerebral small vessel disease with the development of depressive symptoms.[26-29] In addition, post mortem research in late-life depressed patients has demonstrated pathological changes of cerebral blood vessels and an up-regulation of inflammatory markers in depression-related brain areas, suggesting an etiological role of ischemic vascular pathology.[30] The vascular depression hypothesis might also be applicable to other somatic conditions with concurrent vascular abnormalities, such as hypertension and CKD. To date, this has rarely been evaluated.



White matter hyper-intensities on MRI (source: DIP study)

relatively young individuals. In addition, we found that hypertension without depression was not associated with reduced brain volumes. Moreover, the mean age of depression onset was lower than the mean age of hypertension onset. An alternative pathway that may be more likely is that the generic association of depression and hypertension with regional gray matter volumes reflects a pre-existing shared vulnerability. If brain regions involved in emotional and autonomic processes were developed abnormally, or changed for instance due to (chronic) stress,[14-17] this could render individuals vulnerable to develop hypertension[8] as well as depression.[18]

Studying brain structure in a sample with advanced somatic disease increases insight in the potential role of acquired brain injury in depressive symptoms. CKD is associated with high vascular burden, structural brain abnormalities, and increased depression prevalence.[31,32] In ***chapter 4***, we observed a significantly greater white matter lesion severity and lower gray matter volume in patients with CKD compared to age- and sex-matched controls. Consistent with the vascular depression hypothesis,[10,11] region-specific examinations suggested that structural alterations were localized in depression-related brain areas. White matter lesions were observed in the frontal lobe and in the periventricular frontal caps. In addition, gray matter volumes tended to be lower in frontal areas, i.e. clusters in the orbitofrontal cortex. Interestingly, this was most pronounced for patients with depressive symptoms, as we found additional clusters in the orbitofrontal cortex and inferior frontal gyrus for this group. All these findings were, however, not statistically significant after correction for multiple comparisons. The lack of power in this exploratory study precludes drawing firm conclusions. The observations could be indicative of an increased vulnerability to develop depressive symptoms in the context of CKD. Nonetheless, we cannot exclude the possibility that these regional lower volumes reflected a pre-existing vulnerability instead of a pathophysiological consequence of CKD. In addition, it should be mentioned that CKD and dialysis are associated with a complexity of pathophysiological processes that could affect the brain. Therefore, other processes than vascular pathology (e.g. inflammation and tryptophan depletion) can also potentially lead to brain alterations and subsequent depression.

Non-causal pathway: the confounding role of prognostic factors

Because depressive symptoms overlap with symptoms of somatic disease, the possibility should be explored that depression merely reflects the somatic disease. Disease severity could confound the association between depression and poor medical prognosis in patients with co-morbid somatic disease.[33] In ***chapter 5***, we assessed the association between depression and cardiovascular (CV) prognosis while adjusting for Global Registry of Acute Coronary Events (GRACE) score, a

well-validated composite score for post myocardial infarction (MI) mortality risk.[34-36] We found that, although depressive symptoms were related to GRACE score, GRACE score explained only part (28%) of the relation between depression and CV prognosis. Depression remained an independent predictor of CV prognosis after adjusting for GRACE score. This is consistent with previous studies that adjusted for various (combinations of) clinical factors related to prognosis.[37] Our secondary analyses showed that somatic/affective depressive symptoms, but not cognitive/affective depressive symptoms, were related to GRACE score. GRACE score partly attenuated the relation between somatic/affective depressive symptoms and CV prognosis. In line with most previous studies, we therefore concluded that somatic/affective depressive symptoms predict CV prognosis independent of prognostic factors related to the disease.[38,39]

Nevertheless, although GRACE score has high predictive value for mortality after a MI,[36] the possibility of unmeasured and residual confounding of disease-related prognostic factors remains. More specifically, a number of prognostic factors that would have provided further prognostic information (e.g. inflammation and troponin levels) were not included in the GRACE score, as the accuracy of the GRACE score was balanced against the ease of use for clinical practice.[40] In addition, clinical variables are never measured perfectly accurately and some continuous measures were dichotomized in the GRACE-model. Therefore, the confounding role of the GRACE-variables in the association between depression and prognosis was probably underestimated. In other words, depression may in reality be more a reflection of the disease than we were able to demonstrate.[41]

Behavioral pathway: cardiac rehabilitation, depression, and mortality risk

In ***Chapter 6*** we observed that depressed MI patients benefited significantly more from cardiac rehabilitation (CR) than non-depressed patients, in terms of mortality rates. CR was associated with a significantly lower mortality rate only in depressed patients. This was after adjustment for confounding factors, including age, sex, and MI severity markers. No association of CR with survival could be demonstrated for patients without depressive symptoms.

These findings indicate that poor adherence to CR programs[42-44] is not likely to explain the increased mortality risk for post-MI depressed patients.[45] The observation that depressed patients benefited specifically from CR may be because they had more to gain, due to worse initial health behaviors,[46,47] worse initial pathophysiology, or both. Notably, in addition to improving cardiovascular health, CR has been found to reduce depression.[48] Possibly, therefore, the beneficial effects of CR on mortality may be mediated by the improvement of depression. This suggestion concurs with some observational studies in coronary artery disease (CAD) and heart failure patients.[49,50,51] These studies indicated that CR was specifically related to lower mortality rates if depressive symptoms

improved, and this was mediated in part by positive effects of exercise. However, a disease management program in heart failure (HF) patients, resulted in a trend for *higher* incidence of readmissions and mortality in depressed patients.[42] Notably, that intervention solely consisted of education and support and did not include exercise training and group meetings.

Our findings as well as those of others[42-44,49-52] suggest that lifestyle behaviors are likely important in the association between depression and medical prognosis. Our finding that the non-participating half of the depressed patients had the highest mortality rates (see Kaplan Meier curves in chapter 6), could have been the result of unhealthy lifestyle habits. In line with this, a study in stable CAD patients found that lifestyle factors, particularly physical activity, explained almost half of the association between depression and new cardiovascular events.[53] Taken together, our findings implicate that depressed patients should particularly be encouraged to attend CR to improve cardiac prognosis.

Integration of the findings in a broader perspective

In conclusion, the results of this thesis indicate that depression is probably not merely a psychological consequence or a reflection of the somatic disease. Although these aspects may play a role, additional biological and behavioral factors are likely to be involved in the bi-directional relation between depression and somatic disease.

The findings described in this dissertation should be interpreted in the broader context of interactive models about the etiology of psychopathology.[54] According to such models, depression is a multifactorial condition which results from an interplay of biological, psychological, and social factors.[54,55] When vulnerable individuals (e.g. personality, genetic profile, pre-existing cognitions) are exposed to stressful events, this may trigger the onset of depression. In this view, the presence of a somatic disease can be regarded as a stressor that could result in depression in vulnerable individuals. Mechanisms of how this stressor could result in depression may be related to the meaning of the somatic disease (e.g. life-threat), or to its consequences (e.g. disability, social isolation), or to biological processes (e.g. brain changes, inflammation). In the other direction, depression in itself is also thought to induce somatic disease, presumably through behavioral and biological pathways.[6,46,56,57] In addition, there may potentially be a mutual vulnerability factor that underlies both depression and somatic disease. In summary, a complex of interactive pathways underlies the comorbidity of depression and somatic diseases.

Importantly, depression is a heterogeneous disorder, in which the etiological basis is likely to differ between individuals. For instance, it has been conceptualized that depression with a first onset late in life is etiologically different from depression

with a first onset early in life.[10,58,59] Late-onset depression is more often associated with cognitive impairment, poor treatment response, vascular risk factors, and no family history of depression.[10,59] In line with this, depression that manifests before the onset of a somatic disease is potentially of a different etiological subtype than depression that develops after the onset of a somatic disease. Predisposed vulnerability for depression, for instance, might be stronger in "pre-" rather than "post-onset" depression.[60] Probably, in "pre-onset" depression, specific behavioral factors (e.g. poor diet and low physical activity) and pathophysiology (e.g. HPA-axis- and sympathetic over-activity) that are related to depression may increase the risk of developing somatic disease.[6,46,56,57] In turn, the psychological consequences of somatic disease may induce or exacerbate depressive symptoms in these vulnerable individuals.[61] On the other hand, it can be speculated that in those who develop depression for the first time after the onset of a somatic disease, biological factors arising from the somatic disease are particularly important. Pathophysiological processes may for instance lead to alterations in mood-related brain areas and thereby inducing depressive symptoms.[10,11,19] In addition, in some individuals "post-onset" depression may be in part a reflection of the somatic symptoms of the somatic disease. However, as biological factors (e.g. inflammation, heart rate variability) as well as somatic symptoms e.g. (fatigue, loss of appetite) overlap for depression and somatic disease, it is difficult to determine directionality.[6,62] Figure 2 depicts the hypothetical model in which different etiological pathways may dominate in subgroups of somatic depression, based on differences in the time of onset of a first depression relative to the onset of the somatic disease.

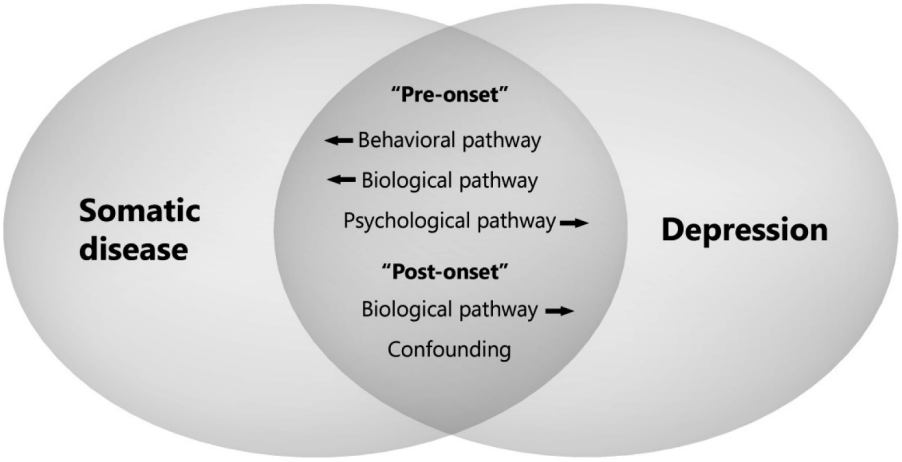


Figure 2: Hypothetical model: different etiological pathways may dominate for somatic depression that develops before or after the onset of a somatic disease ("pre-onset" versus "post-onset")

Furthermore, different depression subtypes are likely to be characterized by different depressive symptom profiles and courses.[63] Based on this idea, Ormel and De Jonge proposed an integrative model of depression in the context of CAD.[63] This model distinguishes two post-MI depression subtypes with different depression symptomatology, courses, and underlying etiologies. The cognitive/affective subtype was proposed to be related to the meaning of the MI and to result from a vulnerability to stressful life events (resembling "pre-onset" somatic depression). This subtype can be viewed as an adjustment disorder that is mostly associated with a less chronic course and better outcomes than the proposed somatic/affective subtype. The somatic/affective subtype was hypothesized to be directly related to underlying pathophysiological processes of the disease (resembling "post-onset" somatic depression), and if persistent, to be associated with poor cardiac outcomes. Our findings that only somatic/affective depressive symptoms were related to GRACE score and to poor CV prognosis are in consonance with this theory. Furthermore, poor health behaviors were proposed to accompany persistent depression, and to mediate the effect on CAD prognosis.[63]

Interestingly, the model by Ormel and De Jonge may explain why traditional depression interventions were not successful in improving CAD prognosis.[63,64] Namely, these interventions, including CBT and antidepressant medication, were not directed at improving the underlying pathophysiological processes of the high-risk somatic/affective subtype and the poor health behaviors related to persistent depression. Otherwise, CR directly (exercise training) and indirectly (educating health behaviors) interferes on underlying somatic processes. Therefore, according to the model[63] and the current results, CR may be more promising in improving (somatic) depressive symptoms and cardiac prognosis than traditional anti-depressant interventions alone. Moreover, CR additionally focuses on psychological aspects, as it generally also includes individual meetings with a nurse, social worker, or psychologist. Plausibly, integrating the management of medical and psychological aspects will be most effective. This was also indicated by a collaborative care trial, in which intervention in both medical and psychological aspects, improved medical as well as depression outcomes for patients with diabetes and CAD with comorbid depression.[65]

Methodological considerations

Causal interpretation was limited in this dissertation, as the results were all based on observational studies, mostly with cross-sectional designs. We were therefore not able to infer whether depression was a cause or a consequence of diabetes in chapter 2. In line, we do not know whether the observed brain differences in chapters 3 and 4 were a cause or a consequence of either depression or somatic

disease. Furthermore, unlike intervention studies, observational studies are prone to unmeasured confounding. This limitation should be especially considered for chapters 5 and 6, in which we respectively investigated the extent of confounding by GRACE score and the effect of CR in the relation between post-MI depression and prognosis. Because participants were not randomized to CR (chapter 6), unmeasured factors and selection bias could have affected the findings.

Another important methodological consideration is that, due to the complex interplay between biological, behavioral, and psychosocial factors, it is impossible to completely disentangle the pathways that potentially link depression and somatic disease. For example, as the psychological meaning depends somewhat on the pathophysiological severity of the disease (the confounder), adjustment for disease severity markers may result in overcorrection. Consequently, in chapters 2 and 5 we might have removed a significant part of the psychological impact of respectively diabetes and MI by adjusting for prognostic markers. In line with this, in chapter 4 it remains unclear whether the indicated brain alterations may be a mediator between CKD and depressive symptoms, or merely a marker (confounder) of worse underlying CKD severity, which in turn is related to depression. Thus, although our findings indicated a role for biological factors in the association between depression and somatic disease, a plausible additional role for psychological factors related to the disease cannot be excluded.

Furthermore, because of the heterogeneity of depression in the context of somatic diseases, the relative contributions of biological, behavioral, and psychosocial factors to somatic depression are likely to be different for separate individuals.[15,61,66] Different etiological pathways may underlie post-MI depression for individuals with different symptom profiles.[63] As a result, factors that may mediate the association between depression and somatic diseases are also likely to differ across individuals. For instance, somatic but not cognitive depressive symptoms were related to GRACE score and CV prognosis (chapter 5). When this heterogeneity in depression is not taken into account in the analyses, i.e., examining the sample as a whole instead of discriminating between patients with different characteristics (e.g. based on symptomology), the strengths of contributing pathways to somatic depression in individuals may be underestimated. This is a potential explanation for the lack of significant findings regarding structural brain abnormalities in depressed versus non depressed CKD patients (chapter 4).

Furthermore, a direct (matched) comparison between depression with and without CKD would have given more insight in the role of brain abnormalities in the etiology of depression in the context of CKD (chapter 4). Actually, this was the original goal of the DIP study. We aimed to include 24 matched depressed individuals with and 24 without CKD, and similar numbers of non-depressed individuals with and without CKD as control groups. Unfortunately, less CKD patients than expected met our inclusion criteria. Although we expanded our

recruitment possibilities and broadened our inclusion criteria, we were eventually only able to include 10 depressed and 14 non-depressed CKD patients. The most important reasons for lack of inclusion were MRI-contraindications and too high disease severity (according to the physician or patients themselves). Additionally, these recruitment difficulties resulted in a selection bias towards the healthiest CKD patients. Unfortunately, direct comparison of the brains of depressed participants with and without CKD was not possible, because they were not matched on important confounders such as sex, age, and education level. Nonetheless, with our data we were able to find indications that CKD was associated with structural abnormalities in depression-related brain areas (chapter 4). In addition, we have collected a rich dataset, consisting of various functional and structural MRI scans, cognitive tasks, and questionnaires, in which innovative future studies can be performed within the CKD group (N=24) and the depressed group without CKD (N=24) separately.

Additionally, we used different somatic diseases to investigate the relation between somatic disease and depression. Therefore, generalizations of the findings towards other patient populations are debatable. Nevertheless, the somatic diseases in this thesis are highly inter-related and have some shared underlying pathophysiology. Importantly, depression is consistently associated with a whole range of chronic somatic diseases, in which it generally increases the risk for poor medical outcomes.[67-69] It should also be noted that we used different assessments of depression. Questionnaires, more than diagnostic interviews, may reflect somatic disease distress and might pick up somatic complaints reflecting the severity of the somatic disease.[70,71] Still, both types of assessments have been consistently associated with somatic disease and demonstrated to be predictive for poor medical prognosis.[31,72,73]

In the current dissertation, MRI was used to evaluate structural brain differences as a pathway in the relation between somatic disease and depression. Although this yielded valuable information, as a result of limitations in spatial resolution MRI provides no direct insight in the neuropathological basis of the observed differences. By combining knowledge derived from post-mortem studies, the underlying etiology of abnormalities observed in MRI research might be better understood. For example, studies in postmortem tissue from (older) depressed patients identified pathological changes of cerebral blood vessels, up-regulation of inflammatory markers, and changes in number and volumes of glial cells and neurons in frontal-subcortical structures.[74] This is congruent with the localization of depression-related alterations, visualized with MRI.[9,75]

Directions for further research

Most of the associations found in this dissertation were based on cross-sectional observational studies. In order to draw causal conclusions, prospective studies are needed. Given the complexity of interactive pathways that underlie the comorbidity of depression and somatic disease, identification of a straightforward underlying mechanism will not be likely. Nevertheless, it remains important to elucidate the understanding of contributing pathways, as this might provide new avenues to improve treatment.

To enhance our understanding of the interplay of different pathways underlying somatic depression, these should ideally be studied in concert. For this purpose, a prospective population-based study with a multidisciplinary design could be used to follow initially healthy individuals over a long period of time. The LifeLines study, for example, enables research on the interaction between behavioral factors, psychosocial aspects, and (neuro)biological disturbances, that could contribute to the development of somatic depression.[76] As MRI is not part of the protocol in Lifelines, it would be interesting to repeatedly scan a nested (high risk) subsample of LifeLines. In that way, it could be examined whether brain differences already exist between depressed and non-depressed persons in early stages of somatic disease. Also, it could be evaluated whether progression of structural brain abnormalities is followed by incident depression. In relation to this, other biological markers (e.g. inflammation and cholesterol levels), lifestyle behaviors (e.g. diet habits, physical exercise, adherence, and engaging in CR or disease management programs) and psychological aspects (e.g. depression symptomatology) can be prospectively evaluated. In addition, comparing these factors between depressed individuals with and without somatic disease would provide additional insight into a potential distinctive depression etiology (the original design of the DIP study).

In addition, such a multidisciplinary prospective study is suitable to characterize potential distinctive subgroups of depression, in order to optimize detection, prevention, and treatment approaches. It would for instance be interesting to evaluate the hypothetical model depicted in figure 2, which proposes different etiological depression subtypes based on the time of onset of a first depression relative to the onset of the somatic disease. Other candidate features to take into account when examining subtypes are age, family history of depression, depression course and symptomatology (e.g. somatic and cognitive symptoms), antidepressant treatment response, cognitive function, and multimorbid medical diseases. For clinical purposes, it may be further characterized what mechanisms underlie the beneficial effects of CR on prognosis, and what aspects of CR might be particularly beneficial for subgroups of patients. For instance, it would be interesting to evaluate whether the beneficial effects of CR

on mortality may be mediated by the alleviation of somatic depressive symptoms. This would be in line with our findings that specifically somatic symptoms were associated with GRACE score and poor CV prognosis.

Clinical implications

The multifactorial and heterogeneous etiology of somatic depression should be taken into account in order to translate the findings to clinical practice. In other words, interventions should ideally target multiple potential pathways that underlie somatic depression and should be adjusted to the needs of individual patients.[65] To date, traditional depression interventions in CAD patients only had a small effect on depression outcomes, and were not successful in improving CAD prognosis.[64] In line, no substantial benefits of traditional depression interventions on depression and medical outcomes were observed for depressed diabetes and CKD patients.[77,78]

Interestingly, structural brain alterations as well as neuropsychological functioning were found to be predictive of treatment non-response in late-life depression.[20,79] These predictors were also highly related to vascular risk factors.[20,79] Probably, preventing the development and progression of cerebrovascular damage and improving physical health will be more effective to enhance depression and medical prognosis than traditional depression treatments alone. Interventions should for instance additionally target the underlying vascular disease and its risk factors. In line with this suggestion, our results as well as those of others [51] indicated that CR was associated with reduced mortality rates in depressed MI patients. Exercise training and interventions on unfavorable lifestyle behaviors (i.e. improving adherence, diet, and physical activity) are important aspects of CR that are likely also effective for depressed patients with other somatic diseases. Of interest, exercise has been shown to reduce inflammation,[80] to improve brain structure and function, in particular in subcortical-frontal brain areas, and to improve cognitive function and reduce depressive symptoms. It is noteworthy that exercise therapy has generally been found to reduce depressive symptoms in patients with and without cardiac disease, with similar efficacy as traditional depression therapies.[48,81,82]

Furthermore, cerebrovascular drugs (i.e. nimodipine), transcranial magnetic stimulation, and carotid stent placement have been found promising to improve depressive symptoms in patients with vascular depression.[83,84] Further trials are needed in order to replicate these findings and to evaluate the efficacy of a broader range of cerebrovascular drugs that can improve the perfusion of the brain and thereby possibly improve depressive symptoms. Whether preventing vascular disease at an earlier age may reduce the risk of incident depression is another potential area of future research.

In order to apply individual-tailored interventions, recognition of patients who are at risk for developing comorbid depression and somatic disease is important. For instance, considering older patients with treatment-resistant depression, it may be useful to incorporate systematic monitoring of vascular risk factors, such as cholesterol, glucose, and blood pressure levels in standard practice, and to promote favorable lifestyle behaviors.[65] On the other hand, although screening for depression in patients with a somatic disease is a subject of debate,[85] our finding that CR was associated with lower mortality rates specifically for depressed patients, suggest that screening for depression may be valuable.

Concluding remarks

Depression in the context of somatic diseases is very common and is associated with a poor quality of life and poor medical outcomes. This dissertation aimed to provide a better understanding of the association between depression and somatic disease. The findings indicate that depression is not merely a psychological consequence of the disease, but that biological and behavioral factors probably also underlie the bi-directional relation with somatic disease. Interventions targeting both the psychological and physical health of patients with somatic depression are therefore likely to contribute to the improvement of depression as well as medical outcomes. Importantly, for both research and clinical purposes, it should be considered that the etiological pathways to comorbidity are complex and intertwined, and likely different for subgroups of patients. Hopefully, a multidisciplinary research approach, in which the interplay of different pathways are taken into account, will further contribute to a clearer picture of depression in the context of somatic disease.

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