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# Chapter 7

Summary and general discussion

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### Background

The work in this thesis focuses on investigation of the appearance of depression in later life. Although a different presentation of late-life compared to early-life has been suggested for many decades, it remains unclear whether this really is the case. Explanations for a possibly different clinical presentation of late-life depression include the co-occurrence of depression and age-related somatic diseases. Our studies focus on the impact of age and somatic diseases on the appearance of late-life depression. Somatic diseases in older age may affect both the symptom profile and the course of depression. On the other hand, symptoms of somatic diseases may be mistaken for somatic symptoms of a depression. In this thesis, we aimed to establish whether there is an age-related presentation of depression and to further unravel the appearance of late-life depression in relation to somatic comorbidity.

### Summary of the results

#### *Presentation of late-life depression*

As a starting point, we performed a meta-analysis on age-related differences in the phenomenology of depression (**Chapter 2**). In line with our expectations, the study showed that some symptoms of early-life and late-life depression differed, but not all of them. For example, compared to early-life depression, late-life depression presented with more agitation, general and gastrointestinal somatic symptoms and hypochondriasis, and with less feelings of guilt and less loss of sexual interest. However, because older people often lack a partner and often have decreased sexual desire and functioning, this might explain why loss of sexual interest was less often reported in late-life depression. Moreover, we could not rule out that some of the differences in the occurrence of the 'somatic' symptoms of depression were 'untrue' differences, due to the overlap of somatic symptoms of depression and age-related somatic comorbidity at old age.

The study in **Chapter 3** aimed to establish symptom dimensions and corresponding subscales of late-life depression underlying the Inventory of Depressive Symptomatology Self-Report (IDS-SR) in older depressed and non-depressed persons. We found that, in older people, the IDS-SR measures three homogeneous symptom dimensions reflecting a mood, a somatic and a motivational symptom domain. The *mood symptom dimension* contains the IDS-SR items: feeling sad, feeling irritable, feeling anxious or tense, reactivity of mood, quality of mood, future pessimism, suicidal thoughts, panic or phobic symptoms, and interpersonal sensitivity. The *somatic symptom dimension* consists of the IDS-SR items: initial and middle insomnia, early morning awakening, appetite disturbance, weight disturbance, interest in sex, aches and pains, and sympathetic arousal. Finally, the *motivational symptom*

*dimension* includes the IDS-SR items: sleeping too much, self-criticism and blame, interest in people/activities, energy/fatiguability and psychomotor retardation. We showed that these symptom dimensions can be used as IDS-SR-subscales and are generalizable to a broad older population, as our sample reflects the different stages of depression, as well as healthy controls, different healthcare settings, and a wide range of older ages. Importantly, the IDS-SR subscales are specific for older people, as they differ from the previously found symptom dimension used in younger persons.<sup>1</sup> The use of these dimensions to distinguish different symptom profiles within late-life depression may benefit both clinical practice and related research.

Our meta-analysis revealed a more somatic presentation of late-life compared to early-life depression. However, the question as to whether it was an 'untrue' found more somatic presentation due to misattribution of symptoms of age-related somatic diseases to depression was not answered in that study. **Chapter 4** describes the results of our study on the influence of somatic diseases and age on the presentation of late-life depression using the three IDS-SR subscales as described above. Both depressed and non-depressed older persons were included to differentiate between the presentation of depressive symptoms due to somatic diseases and higher age in their own right, and in relation to depression. We found that neither a higher somatic disease burden nor higher age contributed to more somatic symptoms of late-life depression itself. This finding is in contrast with other studies suggesting a more somatic presentation of depression in later life; however, these studies did not take into account the possible misattribution of symptoms of comorbid somatic diseases to depression.<sup>2,4</sup> Further, our finding that depressed older old persons aged  $\geq 70$  years tend to show less mood symptoms is in line with other studies that compared older and younger depressed persons with age cut-offs between 65-75 years.<sup>2,5,6</sup> Remarkably, we found a decrease in symptom severity of the motivational symptom dimension with higher age, in contrast to the high prevalence of apathy in our depressed cohort found by others.<sup>7</sup> However, our motivational symptom dimension included the symptoms sleeping too much, self-criticism and blame, interest in people/activities, energy/fatiguability and psychomotor retardation, which apparently does not represent the concept of apathy as defined by Marin and Starckstein.<sup>8</sup> Actually, our finding of less symptoms of the motivational symptom dimension in depressed older old persons aged  $\geq 70$  is partly in line with our meta-analyses and other studies that found less feelings of guilt in later life.<sup>9-12</sup> Alternatively, the generally found increase of apathy in late-life depression may be the consequence of a decline in cognitive functioning rather than of increasing age.

Our finding of less mood symptoms in our older group of depressed persons (i.e. aged over 70 years) raises the question as to whether this is a result of not *experiencing* or not *reporting* a sad mood. The few articles that have discussed this issue reported conflicting

opinions. It is possible that the current cohort of older persons is not accustomed to, or is ashamed to express a sad mood and, instead, expresses somatic symptoms of depression.<sup>13,14</sup> Another possibility is that older persons more often consider a sad mood to be a normal part of their aging life. On the other hand, it is argued that depressed older persons may present with medically unexplained somatic symptoms, hopelessness or apathy, due to not experiencing a sad mood.<sup>6</sup> In fact, a prospective cohort study on this topic found that, compared to younger persons, older persons reported less sadness as measured with the CIDI. Remarkably, the younger cohort, 13 years later, reported sadness in the same way as the older cohort did before.<sup>15</sup> This suggests that the age-related differences found in reporting depressive symptoms cannot be explained by a cohort effect. At the same time, it was found that older depressed persons often do not report any depressive symptoms to their GP, in contrast to what was reported in a research interview.<sup>16</sup> However, our findings are not based on information gathered from a GP, but on reported depressive symptoms of the IDS-SR which were measured in an interview during the NESDO baseline assessment. Therefore, our finding of less reported mood and motivational symptoms based on the IDS-SR obtained from an interview seems even more valid, as in daily practice older depressed persons might spontaneously report even less mood and motivational symptoms to their GP, than found in the present study.

#### ***Somatic (co)morbidity in late-life depression***

The study in **Chapter 5** aimed to further clarify the relation between depression and somatic diseases with respect to the impact of chronic somatic diseases on the course of late-life depression. In line with previous studies, we confirmed that the overall somatic disease burden is associated with the presence of depression at 2-years follow-up.<sup>17,18</sup> Also, a chronic severe course of depression was more often found with increasing overall disease burden. In particular, the presence of both cardiovascular disease and musculoskeletal disease was associated with a depression at 2-year follow-up and with a chronic severe course of depression. Furthermore, a chronic course of depression with variable severity was more often found in the presence of chronic non-specific lung diseases and cancer. Thyroid and gastrointestinal diseases were not associated with a chronic or recurrent course of depression at 2-year follow-up.

**Chapter 6** presents the results of our study examining the presence of cardiovascular diseases in relation to both loneliness and late-life depression. Loneliness and cardiovascular diseases were associated only in females, but the presence of depression explained this association. Unexpectedly, we found no relationship between loneliness itself and cardiovascular diseases, neither in the presence nor absence of depression. Until now, few studies have examined the relation between loneliness and cardiovascular diseases. These

studies, except for one,<sup>19</sup> were not in line with our results.<sup>20-22</sup> However, in those studies depression was not adjusted for, whereas our study showed that depression can be a confounder for the relation between loneliness and cardiovascular disease.

### **Methodological considerations**

This thesis comprises the results of a meta-analysis that was based on 11 studies including more than 2000 participants, as well as the results of four studies that used data from the NESDO and included 510 participants. The design of the NESDO studies was observational, most were cross-sectional studies and one study had a longitudinal design. A cross-sectional observational design is suitable to answer our research questions on the presentation of depression and to define symptom dimensions of the IDS-SR in later life. However, due to its cross-sectional design no conclusions can be drawn about possible causal relationships between these associations, e.g., between loneliness and cardiovascular disease in depressed and non-depressed older persons. Of course, it may be even more valuable to examine this research question in a long-term cohort study covering several decades. After all, a long-term exposure to loneliness or depression seems inevitable when it comes to a possible risk factor for (cardio)vascular disease at older age. For instance, a 40-year longitudinal study showed that depression at younger age was a risk factor for death from stroke at older age.<sup>23</sup> However, in line with our finding, a 20-year longitudinal study that followed older persons from age 70 until 90 years did not find an increase of mortality or morbidity in the presence of loneliness.<sup>24</sup>

In this thesis we had the opportunity to use data from the NESDO sample consisting of both healthy and somatically ill older persons, as well as formally diagnosed depressed and non-depressed older persons, enrolled from primary health care, outpatient mental health care and inpatient mental health care. Therefore, we were able to examine symptoms that were related both to somatic diseases and depression. Furthermore, to our knowledge, no other study has examined the course of formally diagnosed depression in older persons with and without specific chronic somatic diseases. The few studies that have examined specific somatic diseases in relation to depression were mostly performed among a somatically ill population only, or investigated depressive symptoms in a general population.<sup>25,26</sup> However, some critical questions and remarks are also warranted. Firstly, it is possible that, in some cases, depression has been wrongly diagnosed due to misattribution of symptoms of somatic diseases to depression. In that case, bias might have occurred which, however, seems unlikely. In NESDO, depression was formally diagnosed using the CIDI, which only counts a symptom as diagnostic for the presence of depression if it is not caused by a physical illness. Also, our finding of less severity on the mood and motivational dimension with increasing age was found in the depressed subgroups with both a lower and higher

somatic disease burden. Secondly, because the IDS-SR subscales were established in an older population, it was not possible to compare symptom profiles of depression between older persons and younger persons below the age of 60 years. Thirdly, another unavoidable issue of a cohort study among an older population is the expected high attrition rate due to death or disability. In the NESDO, one-fifth of all participants were lost during the 2-year follow-up. Death and cognitive problems were the most important reasons for attrition in the depressed group, whereas having no interest or time were the most important reasons for the non-depressed group. Only the depressed group was included in our study on the course of depression at 2-year follow-up. Despite the fact that attrition was (as expected) higher in the depressed group compared to the non-depressed group, attrition was not regarded as high compared to other cohort studies in older populations.<sup>17</sup>

### **Clinical implications of our study**

The findings of our study may have contradictory clinical implications. Our results imply a more somatic presentation of depression with higher age, because a decline of mood and motivational symptoms goes together with a relative increase of somatic symptoms. This may result in *underrecognition* of late-life depression in clinical practice because (non-psychiatric) physicians may not suspect depression as an explanation for the presented somatic complaints. On the contrary, in case a depression rating scale is being used, an *overestimation* of late-life depression may be the result due to misattribution of symptoms of somatic diseases (and sickness behavior) to depression.

### ***Back to the case report***

A masked appearance of depression due to a more somatic clinical picture also applied to Mrs. A. At that time, it was unclear whether she had either not experienced or had not reported a sad mood. However, her family had noticed her negative thoughts and a sad mood; this helped us to eventually diagnose a depression. For Mrs. A., only after she had somewhat recovered from her depression could she adequately answer our questions and confirm that she had indeed experienced a sad mood. Earlier, she had not mentioned being sad to her GP or other physicians. Instead, she presented with somatic complaints that later proved to be part of a depression and, therefore, her depression remained unrecognized.

Indeed, it is known that late-life depression is often not adequately recognized by non-psychiatric physicians.<sup>27,28</sup> Awareness that older depressed persons often do not spontaneously report a sad mood or depressive cognitions, may improve recognition of depression in later life. Therefore, we emphasize the importance of physicians asking patients (and their next-of-kin) about a low mood and depressive cognitions, especially in case of medically unexplained somatic symptoms.<sup>29,30</sup>

Another important finding emerging from our work is that the course of depression is even more unfavorable in the presence of somatic comorbidity. This situation also applied to Mrs. A., who had recurrent bronchitis, heart failure, diabetes mellitus type II and hypertension, as well as a severe course of her depression. Moreover, there were many negative somatic consequences of her depression, resulting in (temporary) functional loss and high costs due to a long hospitalization. Therefore, our finding of an unfavorable course of depression with a higher somatic disease burden emphasizes the need for integrated somatic-psychiatric care for older depressed persons, in whom somatic comorbidity is relatively common.

### ***Assessment of depression and depression severity***

At the same time, we found that overestimation of depression severity may occur in the presence of somatic comorbidity when using a depression rating scale (e.g. the IDS-SR). Depression scales are used for the screening of depression (with cut-off points) and the rating of depression severity in both clinical practice and research. The overestimation of depression may particularly apply to those rating scales that include somatic symptoms of depression, such as the IDS-SR, the Hamilton Depression Rating Scale or the Beck Depression Inventory.<sup>31,32</sup> In the early 1980s, the Geriatric Depression Scale (GDS, 1982) and the Hospital Anxiety and Depression Scale (HADS, 1983) were developed and minimize the impact of somatic symptoms. These rating scales may partly overcome the problem of attributing symptoms of somatic diseases to late-life depression. However, with respect to the IDS-SR, more research is needed to define adjusted (higher) cut-offs of the IDS-SR in older persons, specifically for somatically ill older individuals.

### **Research implications of our study**

In older depressed persons, a higher symptom severity of all three IDS-SR subscales was found in the presence of a higher somatic disease burden. However, this was due to misattribution of symptoms of somatic diseases with respect to the somatic and motivational symptom dimension, whereas a truly higher symptom severity was found for the mood dimension. Therefore, for research purposes, the use of the IDS-SR subscales requires adjustment of the symptom severity scores for somatic comorbidity, but only for the motivational and somatic symptom dimension. If *overall* depression severity as measured with the IDS-SR is adjusted for somatic comorbidity, overadjustment will probably occur. Obviously, when depression rating scales are used for screening purposes they should be followed by a diagnostic research interview to formally diagnose depression according to the criteria of the DSM.

Several solutions have been proposed to solve the issue of attributing symptoms of somatic diseases to a depressive disorder when diagnosing depression according to the diagnostic criteria of the DSM in medically ill (older) people. However, until, now, none of



them are satisfactory.<sup>33</sup> For instance, we think that an *exclusive approach* that ignores the somatic symptoms of depression is inappropriate at old age, since we found that precisely non-somatic symptoms of depression were less pronounced in late-life depression.<sup>34</sup> Also, the overestimation of symptoms of the motivational dimension is not resolved using an exclusive approach. In medically ill older persons, a high specificity and low sensitivity was found based on an exclusive approach, with half of the depressed persons being missed.<sup>34</sup> On the other hand, an *inclusive approach* that uses all the somatic symptoms, even if symptoms originate from a somatic disease, showed a high sensitivity but may result in poor specificity.<sup>34</sup> A *substitutive approach* replaces the somatic symptoms (but not the motivational symptoms) by other depressive symptoms to improve the distinction between depression and somatic diseases.<sup>35,36</sup> Furthermore, an *etiological approach* that counts symptoms towards depression if they are judged not to be caused by a somatic disease, is not easy to carry out.<sup>37-39</sup> Moreover, it is known that we cannot always reliably approximate the origin of a symptom.<sup>34</sup> Therefore, we recommend the use of an *inclusive approach* to ensure recognition of depression in late life.<sup>34</sup> In contrast, an etiological approach is required to formally diagnose depression according to the criteria of the DSM-IV.<sup>40</sup> Admittedly, when using an inclusive approach one must be aware that the diagnostic criteria of the DSM can (possibly) be fulfilled by symptoms of sickness behavior and/or a somatic disease. At old age, however, because unrecognized depression may result in an adverse health outcome it is important to rule depression out. An additional requirement, i.e., that the presence of a sad mood, depressive cognitions (e.g. feelings of worthlessness or guilt) or suicidality is essential, might be a suitable intermediate solution because these symptoms may distinguish depression from sickness behavior and/or somatic diseases.<sup>37,41</sup>

### **Future research on the appearance of depression in later life**

In this thesis, because we aimed to contribute to the unravelling of the heterogeneous presentation of depression, we focused on age-related heterogeneity. The impact of age of onset on the age-related differences found in the presentation of late-life depression was not studied in this work and still needs further examination. Future research should also aim at investigating underlying mechanisms of (age-related) symptom variations within late-life depression (such as biological, psychological and sociological pathways) and how they modify the appearance of depression.<sup>42</sup>

More studies are also needed to improve the recognition of late-life depression, as improved recognition may enhance the outcome of depression and somatic health. Finally, our findings were based on symptoms reported on a depression scale. However, further investigation is needed with respect to experienced symptoms that may not be (or are less spontaneously) reported to a physician, compared to the use of a questionnaire at old age.

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