General discussion
1 AIMS OF THIS THESIS
The aim of this thesis was two-fold. First, we wanted to examine whether late-life MDD differs in presentation, etiology, and prognosis from MDD in younger ages. Therefore, we studied associations between age and respectively a wide range of depressive symptoms (Chapter 2), a variety of well-established risk factors for MDD (Chapter 3), and the two-year course of multiple dimensions of MDD (Chapter 4). Next, we wanted to establish whether biological age was involved in the presentation, etiology, and prognosis of MDD. Hence, we studied associations between telomere length and respectively MDD (diagnosis and characteristics, Chapter 5), early and recent psychosocial stress (Chapter 6), and again the two-year course of MDD (Chapter 7). Data from NESDA and NESDO were combined in Chapter 2, 3, 4, and 7. In Chapter 5 and 6, NESDO data only were used, meaning an older sample (60+ years) was used in these chapters. In the current chapter, a summary of the main findings of Chapter 2 to 7 will be provided, the findings will be discussed within the framework of existing literature, methodological considerations are discussed, and implications for clinical practice and future research are put forward.

2 SUMMARY OF MAIN FINDINGS
Findings of Chapters 2 to 7 are summarized in Table 1. In Chapter 2 we examined whether age differences existed in the presence of 30 individual depressive symptoms of the Inventory of Depressive Symptomatology (IDS-SR)\(^1\) and in the presence of mood, cognitive, and somatic/vegetative symptom clusters. This was examined in 1,404 participants aged 18-88 with a current MDD diagnosis. Interestingly, we found depression severity, indexed by the total score of the IDS, to be stable across the life span. Regardless, 20 (67%) out of 30 symptoms were associated with either younger or older age. Symptoms most strongly associated with older age were early morning awakening, reduced interest in sex, and problems sleeping during the night. Interpersonal sensitivity, feeling irritable, and sleeping too much were most strongly associated with younger age. Looking at symptom clusters, we found a shift over the life course from mood symptoms to somatic symptoms. These findings suggest that not only is somatic health involved in the etiology of late-life MDD,\(^2\) the presentation of MDD in older age is also more somatic. Additionally adjusting analyses for the number of chronic diseases did not reduce the association between age and somatic/vegetative symptoms, indicating our findings are not simply due to a higher prevalence of diseases in older age.

Next, in Chapter 3, associations between age and well-established risk factors for MDD were assessed. Participants (N = 2,215) were aged 18-93 years and either had a current MDD diagnosis, or were healthy controls with no lifetime diagnosis of depression or anxiety disorders. Risk factors under study were socio-economic status (years of education and low income), personality (neuroticism, extraversion, conscientiousness, agreeableness and openness), life stressors (childhood abuse and recent negative life events), social functioning (low social support, loneliness, not having a partner, and social network size), lifestyle (alcohol use, smoking, and physical...
inactivity), and health (body mass index (BMI), pain, and the number of chronic
diseases). We first studied whether the occurrence of these risk factors was associated
with age. Next, we examined whether the strength of associations between risk factors
and MDD diagnosis and depression severity differed across the life span. We found all
risk factors to be differentially associated with age, indicating absolute risks differ across
the life span. We then confirmed the importance of all risk factors for MDD, as all risk
factors were associated with MDD and depression severity. However, some risk factors
turned out to be more strongly related to MDD and depression severity when their
occurrence was least expected. As a result, aspects of poor health (BMI, pain, and the
number of chronic diseases), which are usually linked to late-life depression, were
shown to be more strongly related to depression in ages 18 to 39.

In Chapter 4 we aimed to examine whether the two-year course of MDD
differed across the life span. Participants (N = 1,042) at baseline had an MDD diagnosis
and a score of at least 14 on the IDS-SR, and had a valid assessment of MDD after two
years. We assessed associations between age (age range 18-88 years) and four two-year
depression outcomes: having a diagnosis of a depressive disorder after two years, having
a chronic symptom course during two years, time to remission, and depression severity
change. We found the course of MDD to worsen linearly with increasing age for all four
outcomes. This unfavorable age trend could only slightly be explained by a range of
clinical, social, and health factors known to be involved in the prognosis of MDD.

After establishing that differences exist in various dimensions of MDD across the
life span, in Chapter 5, we examined whether depression was associated with biological
age as well, first in older persons (NESDO) only. In the NESDO study using a sample of
355 currently depressed older persons and 128 never-depressed controls, aged 60 to 93
years (mean age 70.5 years), we examined whether those with depression had shorter
TL, expressed in base pairs, compared to controls. In addition, in currently depressed
persons only, we assessed whether characteristics of depression were associated with
shorter TL. We found depression to be unrelated to TL, with regard to its diagnosis as
well as characteristics. Mean TL was similar among depressed and never-depressed older
persons (bp (SD) = 5035 (431) versus bp (SD) = 5,057 (729) respectively). Within
depressed older persons, TL was unrelated to depression severity, duration of the
longest depressive episode, age at onset of the first depressive episode, co-morbid
anxiety disorders, anxiety symptoms, apathy severity, antidepressant use,
benzodiazepine use, cognitive functioning, and childhood trauma. So, late-life
depression was found not to be associated with accelerated biological age. This is in
contrast with findings in NESDA and in multiple meta-analyses on this topic. Possibly,
cumulative exposure to other TL-damaging factors affected never-depressed controls
throughout life to such an extent that potential effects of late-life depression are
overruled.

Next, in Chapter 6, we went on to study in a similar way whether early and
recent life stressors, which are risk factors for MDD, were associated with TL.
Participants were 496 older adults (mean age 70.6 years) from the NESDO study. We
found that childhood abuse, recent negative life events, and loneliness were not
associated with TL. Having experienced any childhood adverse event was weakly, but significantly, associated with TL. Overall, our findings suggested that TL in older ages is not associated with psychosocial stress. Again, this may be explained by cumulative lifetime exposure to TL-damaging factors. Another explanation is that those with the most damaged TL (for instance due to psychosocial stress) do not reach old age, indicating the current sample may display a healthy survivor effect.

Finally, in Chapter 7, we studied whether biological age, again indexed by TL, was associated with the course of depression. NESDA and NESDO data were combined for this study, so persons aged 18-88 years were included. The same sample selection and outcome measures were used as in Chapter 4, but instead of chronological age, TL was the main predictor. Overall, we found TL to be unrelated to the course of depression, even when adjusting our analyses for relevant covariates often associated with TL-shortening. When adding biological and chronological age in the same model, only chronological age was associated with the course of MDD.
Table 1. Summary of main findings (chapters 2-7): chronological/biological age and the presentation, etiology and prognosis of major depressive disorder.

<table>
<thead>
<tr>
<th>Presentation of MDD</th>
<th>Chronological age (Part 1)</th>
<th>Associations with age?</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 depressive symptoms</td>
<td>2 Continuous chronological age (18-88 years)</td>
<td>11/30 symptoms associated with younger age, 9/30 associated with older age</td>
</tr>
<tr>
<td>Mood symptom cluster</td>
<td>2 Continuous chronological age (18-93 years) + three age groups: 18-39, 40-59, 60+ years</td>
<td>Low income more strongly associated with MDD in 60+ years</td>
</tr>
<tr>
<td>Cognitive symptom cluster</td>
<td>2 Continuous chronological age (18-93 years) + three age groups: 18-39, 40-59, 60+ years</td>
<td>Not differentially associated with MDD across ages</td>
</tr>
<tr>
<td>Somatic symptom cluster</td>
<td>2 Continuous chronological age (18-93 years) + three age groups: 18-39, 40-59, 60+ years</td>
<td>Childhood abuse more strongly associated with MDD in 18-39 years</td>
</tr>
<tr>
<td>Socio-economic status</td>
<td>3 Continuous chronological age (18-93 years) + three age groups: 18-39, 40-59, 60+ years</td>
<td>Not differentially associated with MDD across ages</td>
</tr>
<tr>
<td>Personality</td>
<td>3</td>
<td>Not differentially associated with MDD across ages</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>3</td>
<td>Not differentially associated with MDD across ages</td>
</tr>
<tr>
<td>Life stressors</td>
<td>3</td>
<td>Childhood abuse more strongly associated with MDD in 18-39 years</td>
</tr>
<tr>
<td>Social functioning</td>
<td>3</td>
<td>BMI, pain, chronic diseases more strongly associated with MDD in 18-39 years</td>
</tr>
<tr>
<td>Health</td>
<td>3</td>
<td>Not differentially associated with MDD across ages</td>
</tr>
<tr>
<td>Etiology of MDD</td>
<td></td>
<td></td>
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<tr>
<td>-Prognosis of MDD</td>
<td></td>
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<tr>
<td>Persistent MDD diagnosis</td>
<td>4 Continuous chronological age (18-88 years) + six age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70+ years</td>
<td>Higher odds for persistent (2-year) MDD diagnosis associated with older age</td>
</tr>
<tr>
<td>Chronic MDD course</td>
<td>4 Continuous chronological age (18-88 years) + six age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70+ years</td>
<td>Higher odds for chronic course associated with older age</td>
</tr>
<tr>
<td>Time to remission</td>
<td>4 Continuous chronological age (18-88 years) + six age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70+ years</td>
<td>Lower likelihood for remission associated with older age</td>
</tr>
<tr>
<td>Depression severity change</td>
<td>4 Continuous chronological age (18-88 years) + six age groups: 18-29, 30-39, 40-49, 50-59, 60-69, 70+ years</td>
<td>Smaller decrease in depression severity associated with older age</td>
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### Table 1. (Continued)

<table>
<thead>
<tr>
<th>Presentation of MDD</th>
<th>Biological age (Part 2)</th>
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<td>MDD diagnosis</td>
<td>Measurement of age</td>
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<td>Depression characteristics&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TL continuous in base pairs in persons</td>
</tr>
<tr>
<td></td>
<td>aged</td>
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<td></td>
<td>60-93 years</td>
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<th>Etiology of MDD</th>
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<tbody>
<tr>
<td>Childhood abuse</td>
<td>Measurement of age</td>
</tr>
<tr>
<td>Childhood adverse events</td>
<td>TL continuous in base pairs in persons</td>
</tr>
<tr>
<td>Recent negative life events</td>
<td>aged</td>
</tr>
<tr>
<td>Loneliness</td>
<td>60-93 years</td>
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<th>Prognosis of MDD</th>
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<tbody>
<tr>
<td>Persistent MDD diagnosis</td>
<td>Measurement of age</td>
</tr>
<tr>
<td>Chronic MDD course</td>
<td>TL continuous in kilo base pairs in persons</td>
</tr>
<tr>
<td>Time to remission</td>
<td>aged 18-88 years</td>
</tr>
<tr>
<td>Depression severity change</td>
<td></td>
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<tr>
<td></td>
<td>Association with TL, but only unadjusted and overruled by chronological age</td>
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</tbody>
</table>

<sup>a</sup>depression type, depression severity, duration of the longest episode, number of episodes, age at onset first episode, co-morbid anxiety disorder, anxiety symptoms, apathy severity, antidepressant use, benzodiazepine use, cognitive functioning, childhood trauma. MDD = major depressive disorder. TL = telomere length. BMI = Body Mass Index.
3 DISCUSSION OF MAIN FINDINGS

3.1 Does late-life MDD differ in presentation, etiology, and prognosis from MDD in younger persons?

We showed that MDD does differ in presentation, etiology, and prognosis from MDD in younger persons. In our sample of persons with current MDD (aged 18-88 years, Chapter 2), even though depression severity was stable across the life span, 20 (67%) out of 30 symptoms were significantly associated with age. In general, mood symptoms were mostly present in younger ages, whereas somatic symptoms became more apparent with increasing age.

Our results are in line with previous findings by demonstrating the stability of depression severity over time, and by showing a shift towards somatic symptoms over the life span. However, the number of symptoms that seems to shift across the life span exceeds previous findings, as the meta-analysis by Hegeman et al. only found six (35%) out of 17 symptoms to differ between younger and older persons.

However, in our study, reduced interest in sex was associated with older age, whereas this was previously found to be more common in younger ages. Possibly, this can be explained by the notion that older persons are more apathetic, showing diminished interest in various aspects of life, including sex. This is also supported by our finding that having diminished capacity for pleasure or enjoyment was found to be associated with older age. Showing diminished interest for people/activities, which might also resemble apathy, was not related to age in our study.

Our findings for cognitive symptoms were inconclusive, as were previous findings. Mood symptoms were found to become less common over the life span, although findings were inconsistent for the core symptoms of depression. Interestingly, feeling sad was unrelated to age, even though previous research demonstrated sadness to be less common in older ages.

The shifts in depressive symptoms over the life span found in our study might be the consequence of differential etiologies of depression across the life span. Early depression onset has often been shown to be associated with personality (especially neuroticism), and adverse life events. In older age, the likelihood for a somatic pathway to depression might increase. Neurobiological factors, such as cerebrovascular disease, neurodegeneration, and inflammation, may impact the response of the brain towards stress, and therefore might increase the susceptibility to depression. Late depression onset has indeed been associated with poor health and vascular risk factors.

Several somatic symptoms found to be more common in older ages, such as early morning awakening or aches and pains, may be seen as problems inherent to ageing or the presence of chronic somatic diseases. The occurrence of somatic/vegetative symptoms at older age might explain why late-life depression has been found to be relatively more often underdiagnosed, as older persons experiencing these symptoms may show attribution bias thinking their problems are simply consequences of growing older, and they may not feel the need to seek help. General practitioners may not
always be able to recognize these problems as being part of a depressive episode either.\textsuperscript{12}

\begin{center}
\textbf{CONCLUSION 3.1.1:} Late-life MDD differs in presentation from MDD in younger persons. There is a shift from mood symptoms to somatic symptoms with increasing age, which may complicate the diagnostic process.
\end{center}

Interestingly, in our study on age differences in risk factors for MDD (\textit{Chapter 3}), in which we compared the strength of risk factors in three age groups (18-39 years, 40-59 years, 60+ years), we found aspects of poor health to be more strongly associated with MDD in the youngest age group compared to the older age groups. Even though all risk factors under study were confirmed to be important risk factors for MDD, BMI, pain, and the number of chronic diseases (along with childhood abuse and low income) showed the strongest association with MDD in the age group in which their occurrence was lowest. So, even though the importance of somatic health is stressed in late-life MDD, it may be just as an important risk factor in earlier life.

Although this seems surprising, the so-called “on-time, off-time” hypothesis was postulated,\textsuperscript{13} stating that risk factors for depression may have the strongest impact when their timing is least expected, due to the lack of mental preparation and anticipation for such an event to occur. These findings indicate that the effect of poor health in young age should not be underestimated. When chronic diseases or other aspects of poor health occur “off-time”, at young age, appropriate coping mechanisms may help limit the effect of these somatic problems on depression. Previous studies either found poor health to be associated with older age,\textsuperscript{14} or with young age but only in males.\textsuperscript{15}

We found it plausible that reduced social functioning and recent negative life events were most strongly associated with depression in younger ages, because loss of social contacts and negative life events such as widowhood and other losses may be more common and expected in old age. However, we did not find an “on-time, off-time” effect for reduced social functioning and recent negative life events. Both of these risk factors showed similar associations with depression across the life span, and their occurrence was not uniformly highest in old age. In a previous study performed among participants with physical disabilities, the association between social support and depression was also shown to be independent of age.\textsuperscript{16} The fact that we found the number of negative recent life events to be highest in younger ages and to be equally detrimental with respect to their impact on depression across the life span might have to do with the specific life events included. Possibly, differential associations between recent negative life events and depression across the life span can only be observed when looking at these events separately.

We expected childhood abuse and personality to be especially associated with MDD and depression severity in younger ages as a result of their previously mentioned link with early-onset MDD. Moreover, these concepts per definition cannot occur “on-time” or “off-time”. Indeed, childhood abuse was most strongly associated with depression in the youngest age group. We found personality to be an age-independent
risk factor, however, displaying similar associations with depression in all ages. As personality has previously been shown to affect depression treatment outcomes, it is important to note that personality is relevant for depression across the life span, despite its associations with early-onset depression.

**CONCLUSION 3.1.2:** Although late-life MDD and MDD in younger persons share a wide range of similar risk factors, some risk factors were found to be more strongly associated with the presence of MDD when their occurrence is least expected. This is especially the case for aspects of poor health. Although of higher occurrence, poor health was less strongly associated with MDD in older adults.

After establishing age differences in the presentation and risk factors of MDD, we went on to assess whether age also affected the two-year course of MDD (Chapter 4). We found a more unfavorable course for persons with late-life MDD compared to younger counterparts. This was reflected in a two to three times higher likelihood of still having a depression diagnosis after two years, in a more chronic symptom course, in a smaller likelihood of reaching remission, and in less improvement in depression severity. Overall, we found the likelihood for this more unfavorable course to increase linearly with age. Strikingly, these findings could not be explained by clinical (co-morbid anxiety diagnosis, a higher number of previous episodes, antidepressant use), social (social support, loneliness) and somatic health factors (BMI, pain, number of chronic diseases).

As expected, our overall observations provide growing evidence that older age is indeed associated with a poorer course of MDD. In a previous meta-analysis, Mitchell et al. found middle-aged and older persons to demonstrate rather similar remission rates. Our findings show that when taking more course indicators into account, the view is less optimistic than suggested previously. However, findings may be hard to compare as this is the first study to examine age differences in the course of MDD within a naturalistic design. Combining our findings from Chapter 3, that BMI, pain, and the number of chronic diseases were more strongly associated with MDD in younger ages, with the finding that somatic health factors only slightly explain the poorer course of late-life MDD (Chapter 4), it seems that the importance of somatic health in late-life depression may be somewhat overestimated. It is important to examine which aspects of aging not included in this thesis increase the vulnerability of older persons not recovering from MDD or to unravel underlying mechanisms responsible for this unfavorable trend.

Possibly, our findings can be explained by differences in the efficacy of psychological or antidepressant treatment of MDD. Although we adjusted analyses for antidepressant use, it has been suggested that effectiveness of antidepressants in older age can be harmed as a consequence of medical comorbidity, frailty, and drug-drug interactions. As a large proportion of older persons in our study used antidepressants, this could explain the more unfavorable course of MDD in this age group. Although we were unable to determine whether participants underwent specific psychological treatment, older persons in general are less likely to receive psychological treatment.
This may also be reflected in the high use of antidepressants in older persons in our study.

Also, one of the known factors involved in MDD that was not included in Part 1 of this thesis is reduced cognitive functioning.\textsuperscript{21,22} It has been shown that cognitive decline hampers recovery from MDD and reduces treatment efficacy.\textsuperscript{23} Although suspected dementia and a low score on the MMSE were exclusion criteria for NESDO, we cannot rule out that the presence of early phase dementia in the oldest age groups contributed to our findings. Although we included a range of explanatory health factors, aspects of health not included in our study may be associated with age differences in the course of MDD. For example, specific chronic diseases rather than the number of chronic diseases may be related to a more unfavorable MDD course. Previously, chronic non-specific lung diseases, cardiovascular diseases, musculoskeletal diseases, and cancer have been shown to particularly negatively affect the course of MDD.\textsuperscript{24}

**CONCLUSION 3.1.3:** The two-year course of MDD linearly worsens with increasing age for several course indicators of MDD. Clinical, social, and health factors only explain this unfavorable trend slightly.

**CONCLUSION Part 1:**
Late-life MDD differs in multiple aspects from MDD in younger persons. MDD in later life shows a shift from mood symptoms to somatic symptoms, even though aspects of poor health are stronger risk factors for MDD in younger ages. It also shows a more unfavorable course which can only be explained to some extent by clinical, social, and health factors. The somatic presentation of late-life MDD could be related to underdiagnosing MDD in older persons and should be taken into account in the screening process for MDD. In younger persons, it may be important to provide enough support when chronic diseases or health problems arise, as the lack of anticipation for these events in young age may increase the likelihood for MDD. Future research is needed to unravel which mechanisms are responsible for the worse prognosis of MDD with increasing age. This may go beyond well-established risk factors to date, as these were shown to have little impact on the unfavorable age trend regardless of their association with MDD itself.

3.2 Is biological age involved in the presentation, etiology, and prognosis of MDD?
Over the years, TL has been increasingly associated with psychosocial stress. Since multiple meta-analyses, including studies using NESDA data, showed that shorter TL was associated with MDD in adults (generally under age 65),\textsuperscript{25,26} we first examined whether TL was also related to MDD in an older sample. We specifically studied whether late-life depression (MDD and/or dysthymia) and a range of depression characteristics (depression severity, duration of the longest depressive episode, number of depressive episodes, age at onset of the first episode, comorbid anxiety disorder, anxiety...
symptoms, apathy severity, antidepressant use, benzodiazepine use, cognitive functioning, and childhood trauma) were associated with TL in a sample aged 60 to 93 years. We found no differences in mean TL between persons with late-life depression and never-depressed comparisons, or between subgroups of depressed persons (for instance based on the number of episodes or gradients of depression severity) and never-depressed comparisons. Moreover, within the depressed sample, TL was found to be unrelated to the wide range of depression characteristics under study. Thus, we found no evidence for accelerated TL shortening in late-life depression, indicating we found no evidence for biological age to be involved in the presentation of MDD in older persons.

Although these findings differed from findings in younger adults, compared to previous studies on TL in late-life depression, our null-findings were not surprising. Phillips et al., Huzen et al., and Rius-Ottenheim et al. all previously found TL to be unrelated to depressive symptoms in old age. In older persons with clinically diagnosed MDD, Hoen et al. only found a borderline significant association with TL. In previous studies in younger adults, among which the NESDA study, higher depression severity and longer episode duration have also been found to be related to shorter TL, but our study could not confirm these findings either.

We moved on to examine the association between TL and early and recent psychosocial stress, as life stressors have been associated with shorter TL as well. We assessed whether childhood abuse, childhood adverse events (separation from parents, death of a parent, and parental divorce), recent negative life events, and loneliness were associated with TL, again in a sample of older persons aged 60 to 93 years. Interestingly, childhood adverse events, but not childhood abuse, were found to be associated with shortened TL. We expected similar associations with TL for these concepts, as both have been linked to adverse health outcomes and late-life depression. If anything, childhood abuse was expected to be an even stronger stressor compared to childhood adverse events, as another study previously found an association between childhood abuse, but not childhood adverse events, and psychopathology. Strikingly, we did not even find cumulative childhood abuse (taking into account the frequency and number of types of abuse), or a severe type of childhood abuse such as sexual abuse, to be related to TL. For childhood adverse events we only found having experienced any adverse event to be associated with shorter TL. The three events separately showed to be unrelated to TL. When also taking into consideration that multiple tests were performed and that the p-value for any childhood adverse event would not pass correction for multiple testing, it seems that early psychosocial stress overall is unrelated to TL in older adults.

For recent negative life events, our evidence for an association with TL was limited as well. Although two recent negative life events were significantly associated with TL (being seriously ill, wounded, or a victim of violence; and ending a friendship with a friend, family member, or neighbor), the direction in which they were associated with TL differed. Our findings implied that being seriously ill, wounded, or a victim of violence was associated with shorter TL, whereas ending a friendship with a friend,
family member, or neighbor was associated with longer TL. As loneliness, like twelve recent negative life events, was found to be unrelated to TL, our findings provided little support for accelerated telomere shortening due to recent psychosocial stress. Taken together, although early and recent psychosocial stress are risk factors for MDD, the involvement of biological age in this etiology seems to be lacking in older adults. However, in younger adults such associations have been found previously.39–42

After we established that the course of MDD worsens with increasing chronological age, we were interested to examine whether this unfavorable course was due to differences in biological age. We therefore assessed whether TL was associated with the two-year course of MDD, using the same outcomes as used in Chapter 4 (still having a depression diagnosis, having a chronic symptom course, time to remission, and change in depression severity). For this study, NESDA and NESDO data were combined, enabling us to study TL across the life span. We found TL to only be associated with change in depression severity, but this association disappeared as well after adjusting for clinical, lifestyle, and health variables. When combining biological and chronological age in one model, only chronological age was associated with the two-year MDD course. Thus, biological age could not explain the unfavorable chronological age trend.

Overall, we can conclude in this thesis that biological age is not involved in the presentation, etiology, and course of late-life MDD, even though it may play a role in MDD in younger ages. Several explanations could clarify these contradicting findings. First, like we showed in Part 1 of this thesis, the etiology and presentation of MDD differ across the life span. For instance, we demonstrated that aspects of poor health (BMI, pain, and the number of chronic diseases) were more strongly associated with MDD in persons aged 18-39 years. Perhaps TL is most affected by poor health in these ages as well. However, we found these aspects to be most common in older age. In addition, we showed that MDD in older age is mainly characterized by a range of somatic depressive symptoms. Although one could expect that this higher occurrence of poor health and somatic symptoms leads to a stronger association with shortened TL, TL in older never-depressed comparisons may be affected as well by these aging-related phenomena. Thus, compared to younger ages, differences in TL due to health problems may be smaller between older persons with MDD and never-depressed comparisons of that age. Another possible explanation for the lack of associations between the presentation and etiology of MDD and TL in older persons is that TL itself may be affected differently in older persons compared with adults. In older persons, we found no associations between TL and lifestyle factors, whereas TL has been associated with smoking, BMI, and alcohol use in younger adults previously. Moreover, in Chapter 7, which includes the younger NESDA sample as well, we did find TL to be associated with these factors. The explanation for these inconsistencies is not clear, but in older persons the accumulation of lifetime exposure to biological exhaustion may be of such large magnitude that a single variable, especially one reflecting the current situation such as alcohol use, is not effective enough in affecting TL independently. Also, as suggested by Muezzinler et al.,43 specific events or environmental circumstances belonging to a certain time period may affect an entire birth cohort and may explain differences in TL.

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CONCLUSION Part 2: Biological age, indexed by telomere length (TL), is not associated with the presentation, etiology, and course of MDD in older persons. Possibly, TL of all older persons has suffered lifetime accumulative damage, thereby reducing the independent effects of MDD (characteristics) and psychosocial stressors. Chronological age, rather than biological age, is associated with a more unfavorable course of MDD.

4 METHODOLOGICAL CONSIDERATIONS
The studies included in this thesis have several strengths. By combining the NESDA and NESDO data, two cohort studies that are similar in infrastructures and measurements used, we had access to data from participants aged 18 to 93 years old, enabling us to study MDD across nearly the entire adult life span using a large sample size. Moreover, we were able to study age as a continuous measure in our analyses, contrary to the majority of previous studies in which arbitrary cut-off ages were used to distinguish younger persons from older persons. Another strength is the use of DSM-IV based clinical diagnoses of MDD, often combined with self-report measures of depressive symptoms. We were also able to include a wide range of covariates in order to rule out confounding effects throughout our studies.

However, a number of limitations in this thesis should be pointed out as well. First of all, the majority of studies in this thesis was cross-sectional. Especially when studying age effects, it may be worthwhile to follow individuals for a long period of time in order to observe changes in MDD and its characteristics across the life span. Also, temporality cannot be established, leaving it unclear whether for instance risk factors preceded MDD or occurred because of MDD.

Another limitation is that some studies in this thesis (especially those in Chapters 3, 5-7) may have been affected by a healthy survivor effect. For example, associations between risk factors and older age may have been underestimated because those who suffered the most severe consequences (e.g. due to childhood abuse) may not have survived until old age and may therefore not be included in our study. This may also apply to our studies on TL, as those with the highest telomere attrition may have died...
GENERAL DISCUSSION

prematurely as well. Moreover, studies of Chapters 5 and 6 were only performed within NESDO, meaning only older samples were used in these studies. As such, these chapters have less focus on the life span perspective compared to the other chapters in this thesis.

In the current study qPCR was used to determine TL. Although this method shows good correlation with the Southern blot, another widely used method, qPCR has greater measurement error compared with the Southern blot. Nonetheless, it seems unlikely that the findings in this thesis can be attributed to measurement errors, because the samples of TL obtained were analyzed in the same way for NESDA and NESDO, and previously considerable associations between TL and depression were found within NESDA. TL was obtained from leukocytes, which is non-invasive and an often used method. However, TL is not limited to leukocytes and could be observed in other somatic tissues as well. Nevertheless, Daniali et al. found leukocyte TL to be correlated with TL from skeletal muscle, skin, and subcutaneous fat, which suggests that our results are not limited to leukocyte TL.

The oldest subjects in our studies may have shown age-dependent recall bias, as in older age it may be hard to remember the exact nature of events that occurred earlier in life (such as childhood abuse). On the other hand, overestimation of negative events during life could also occur, possibly as a result of a current negative mood. We did not include extensive data on neurocognitive assessment, as cognitive functioning was assessed differently in NESDA and NESDO. Although our older NESDO sample seemed relatively healthy with only a minority scoring in the range of mild cognitive impairment on the MMSE, and since (suspected) dementia was an exclusion criterion, it may be possible that even milder cognitive dysfunctions may have gone undetected. Therefore, our findings are mainly generalizable to those with normal cognition.

5 IMPLICATIONS FOR CLINICAL PRACTICE

From this thesis it can be concluded that late-life MDD differs in multiple aspects from MDD in younger ages. Interestingly, depression screening and treatment methods are mostly similar across ages.

The fact that MDD in older age is characterized by a range of somatic depressive symptoms, may be the reason that diagnoses of late-life MDD are often missed. As a result, there may be opportunities to improve age-tailored diagnostic methods for MDD to achieve more effective depression screening across the life span. Although it has been suggested that MDD may be difficult to diagnose because over its overlap in symptoms with cognitive impairment, a recent study showed that a widely used diagnostic screening tool in older persons, the Geriatric Depression Rating Scale-15 (GDS-15), is sufficiently able to discriminate depressed persons from non-depressed persons regardless of cognitive impairment. Moreover, including more somatic symptoms in geriatric screening assessments may prove to be ineffective as it could yield to an overestimation of MDD. Therefore, there is a need for the recognition of somatic symptoms whilst preventing that normative aging-related phenomena are classified as MDD as well. An alternative strategy that does not require changes in screening tools is...
to involve caregivers in the screening process. Depressed older persons have the tendency to mainly express somatic complaints rather than psychological or mood symptoms, and observations by caregivers could provide useful additional insight into behavioral changes.

The more somatic presentation is likely to affect treatment outcomes as well. As we also showed that the course of MDD worsens with age, it is important to consider in which way MDD treatment could be improved. Increased attention has been given to the possibilities of collaborative care, especially for late-life depression in the primary care setting. This treatment method would for instance include the involvement of multiple professionals and increased communication between these professionals.

Treatment of MDD may indeed be more effective when not only depressive symptoms are targeted and co-morbid medical problems and social difficulties are addressed simultaneously.

So far, these clinical implications mainly focus on improving diagnosis and treatment of MDD in older adults. However, our study into risk factors for MDD across the life span provided us with leads for the improvement of MDD earlier in life as well. We demonstrated that health factors (BMI, pain, and the number of chronic diseases) often associated with late-life depression, surprisingly, were more strongly associated with MDD in persons aged 18-39 years. As this could be a consequence of the lack of anticipation for such health problems to occur, awareness for the increased risk for MDD caused by health problems in this age group is warranted. For clinicians, it is important to pay attention to or monitor mental health in the context of health problems, for instance after the presence of a new somatic condition is established. Possibly, additional guidance could improve coping strategies and disease management and could help reduce the negative consequences of somatic conditions on mental health, especially in younger persons.

In the past years the potential diagnostic utility of TL as a risk factor for MDD (and other psychiatric disorder) has been increasingly discussed. However, at this point this suggestion may be premature, as evidence for such an association is inconclusive at times. In her thesis “Depression, anxiety, and cellular aging: Does feeling blue make you grey? Josine Verhoeven already noted that in adults aged 65 or younger, only differences in average TL were found between depressed and non-depressed persons. More specifically, due to the high inter-individual variability in TL, some participants among those with the longest TL were depressed, whereas the person with the shortest TL had no lifetime diagnosis of depression. This indicates limited suitability for TL to be used as a diagnostic criterion for MDD. Rather, it seems to be an indicator of general exposure to stress. Moreover, the current thesis showed that TL was not related to MDD and MDD characteristics in persons aged 60 years and older, or to the course of MDD in persons aged 18 to 88 years. Thus, we found little (additional) evidence for the clinical relevance of TL in MDD.
6 FUTURE RESEARCH

The findings discussed in this thesis provide input for future research directions in the field of chronological as well as biological age in the context of MDD. First, we found a shift across the life span from more mood-related depressive symptoms in younger ages to somatic depressive symptoms in older age. However, we were only able to study these symptoms cross-sectionally, indicating we compared persons who are currently young to persons who are currently older. Ideally, future studies follow a young cohort of depressed persons over a long period of time, in order to establish changes in depressive symptoms across the life span within the same population. Moreover, as the somatic symptoms found to be common in older age may be related to underdiagnosing MDD in this age group, it is important to study how the detection of MDD in older age can be improved. Second, we confirmed the importance of a wide range of risk factors for depression, but found some of these risk factors to be age-dependent in the sense that they imposed a stronger risk for MDD in specific age groups. This knowledge could be extended by studying the cost-effectiveness of the prevention of these risk factors, thereby gaining information on which risk factors could best be targeted in which age groups. Third, we found the two-year course of MDD to worsen with age, regardless of the presence of other unfavorable social and health factors. In order to strive for a better course of MDD in older age, it is therefore paramount to unravel which other factors are responsible for this age trend and which could possibly be improved or prevented. This way, we may better understand why older persons have a more chronic course of depression. Fourth, because this thesis showed MDD to differ across the life span, more research is warranted into age-tailored interventions for MDD.

7 CONCLUDING REMARKS

People come in all shapes and sizes. When we go shopping for a new outfit, we make sure to buy garments that perfectly fit our bodies, and this is considered to be normal. So why is it that treatment for depression is similar to a large extent for different populations? Shouldn’t we receive treatment that perfectly fits our minds? This thesis has shown that MDD in late-life (higher chronological age) differs in presentation, etiology and course from MDD in younger ages, indicating there may be different needs and focus points across the life span. It is therefore important to strive towards a more age-tailored approach for depression diagnostics, prevention, and treatment. The clinical utility of TL (biological age) within this picture at this point has not been demonstrated.
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