Major depressive disorder across the life span

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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.

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

Table 1. (Continued)

		Biological age (Part 2)	
	Chapter	**Measurement of age**	**Associations with age?**
Presentation of MDD			
MDD diagnosis	5	TL continuous in base pairs in persons	No association with TL
Depression characteristics[a]	5	aged 60-93 years	No association with TL
Etiology of MDD			
Childhood abuse	6	TL continuous in base pairs in persons	No association with TL
Childhood adverse events	6	aged	Weak association between 'any childhood adverse event' and TL
Recent negative life events	6	60-93 years	No association with TL
Loneliness	6		No association with TL
Prognosis of MDD			
Persistent MDD diagnosis	7	TL continuous in kilo base pairs in persons	No association with TL
Chronic MDD course	7	aged 18-88 years	No association with TL
Time to remission	7		No association with TL
Depression severity change	7		Association with TL, but only unadjusted and overruled by chronological age

[a]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.