1. SUMMARY OF MAIN FINDINGS

This section summarizes the main findings per chapter. The general aim of this thesis was to study associations of depressive and anxiety disorders with markers of cellular aging. More specifically, the first aim was to investigate cross-sectional associations of telomere length with depression and several anxiety disorders. The second aim was to test associations of telomere length with established risk factors of depressive and anxiety disorders, namely childhood trauma and recent stressful life events. The third aim was to provide insights into the longitudinal trajectories of depressive and anxiety disorder and telomere length and mitochondrial DNA (mtDNA) copy number over time. Last, our fourth aim was to shed more light on possible mechanisms underlying the association between depressive and anxiety disorders and telomere length.

In **Chapter 2**, we tested cross-sectional associations between major depressive disorder (MDD) and telomere length in the Netherlands Study of Depression and Anxiety (NESDA). In this study we showed that telomere length was shorter in 1,095 persons with a current 6-month MDD diagnosis (effect size: Cohen's d=0.12; p=.027) and 802 persons with remitted MDD, who had a lifetime history of MDD but no current diagnosis (Cohen's d=0.12; p=.036), as compared to 510 never-depressed control subjects. Further, within the current MDD patients, we showed that both higher depression severity (p=.004) and longer symptom duration in the past 4 years (p=.010) were associated to shorter telomere length, suggestive of a 'dose-response' association.

Chapter 3 consists of a study with a similar cross-sectional design in NESDA. This study showed that 1,283 persons with a current anxiety disorder (social phobia, generalized anxiety disorder and panic disorder with agoraphobia) had shorter telomere length than 582 controls (Cohen's d=0.13; p=.01). Interestingly, 459 persons with a remitted anxiety disorder did not differ from controls in telomere length (p=.84), however, telomere length showed a positive association with time since remission (p=.024). A group of 225 persons who remitted up to 9 years ago had shorter telomere length than 220 persons who were remitted for 10 years or longer (Cohen's d=0.22; p=.022). Furthermore, anxiety severity scores were negatively associated with telomere length in the whole sample, but not in the current anxiety disorder sample only.

The aim of **Chapter 4** was to investigate the cross-sectional association of telomere length with late-life depression in persons older than 60 years from the Netherlands Study of Depression in Older persons (NESDO). Results of this study showed that telomere length did not differ between 355 person with late-life depression and 128 never-depressed controls (p=.59). Moreover, in this sample we found no association between telomere length and symptom severity, duration, age at onset of depression or comorbid anxiety

disorders (all p-values >.20). These null-findings are in contrast with the results of Chapter 2 which described a telomere length-depression association in younger adults.

Chapter 5 concerns a meta-analysis on the link between telomere length and psychiatric disorders, including depressive disorders, psychotic disorders, bipolar disorder, posttraumatic stress disorder (PTSD) and other anxiety disorders, with data from 32 studies (5,289 cases and 9,538 controls). The overall meta-analysis demonstrated a significant effect size (effect size: g=-0.50; p<.001), indicating that psychiatric disorders were associated with shorter LTL. More specifically, subgroup effect sizes were significant for depressive disorders (g=-0.55; p=.004), PTSD (g=-1.27; p=.003) and anxiety disorders (g=-0.53; p=.05), but not for bipolar disorder (g=-0.26) or psychotic disorders (g=-0.23). Meta-regression showed, however, no significant difference in the effect size estimates between the different disorder subgroups. This suggest that shorter telomere length may not be limited to current diagnostic constructs but may instead reflect underlying pathophysiological processes that surpass traditional diagnostic categories.

In **Chapter 6**, we examined the cross-sectional association between early and recent psychosocial life stress with telomere length in 2936 participants from NESDA. This study showed no relationship of childhood life events (p=.805) and childhood trauma (p=.205) with telomere length. However, persons had shorter telomeres if they reported more stressful life events in the past year (p=.028) or up to 5 years ago (p=.018), but not if events occurred more than 6 years ago (p>.10). These results show that the more proximate the psychosocial life stress to telomere length measurement, the more likely they were related. This might indicate that persons are to some extent able to physiologically recover from the effects of psychosocial life stress.

Chapter 7 consists of a review paper that discusses the hypothesis of reversibility of cellular aging in depression. Animal research and in vitro studies provided evidence that recovery of telomere length to some extent is possible. Further, intervention studies including lifestyle changes, stress reduction, social support and psychotropic medications may favorably impact the telomere / telomerase system, possibly by normalizing various underlying physiological dysregulations. However, the evidence is preliminary and no definitive conclusions can be drawn. Large-scale longitudinal or intervention studies that could shed more light on the possibility of reversibility are lacking.

In **Chapter 8** we examined longitudinal associations of depressive and anxiety disorders with telomere length in NESDA. This study with psychopathology and telomere length data of 2936 participants at baseline and 1883 participants at 6-year follow-up showed that persons with current (p=.017) and remitted (p=.046) diagnoses had consistently shorter telomere length compared to controls, confirming our earlier cross-sectional findings. We also showed negative associations between telomere length and the severity

of depressive (p=.007) and anxiety symptoms (p=.009), indicating that the most severe patients had the shortest telomeres. However, changes in the course of depressive or anxiety disorder characteristics over 6 years, were not associated with different telomere attrition rates over 6 years. These results indicate that psychopathology and telomere length do not dynamically change together over time.

Chapter 9 again looked at longitudinal associations, now in the Coronary Artery Risk Development in Young Adults Study (CARDIA) sample. Here, we analyzed data on depressive symptomatology, assessed with the Center for Epidemiologic Studies Depression (CES-D) scale, and two markers of cellular aging, namely telomere length and mtDNA copy number, from 977 persons over 10 years. Results showed that having long-term high levels of depression was associated with shorter average telomere length (p=.038), but no within-person associations were found between changes in depressive symptoms and concurrent changes in telomere length (p=.635). These findings, in line with Chapter 8, suggest that the relation between depression and telomere length reflects a between-person, rather than a within-person, effect. Further, in this study, we did not find evidence for a relationship between depressive symptomatology and mtDNA copy number.

In **Chapter 10**, we tested cross-sectional associations between telomere length and three major physiological stress systems in 2936 participants of NESDA. Physiological stress systems included the immune-inflammatory system, hypothalamus-pituitary adrenal-axis and autonomic nervous system. Results showed that higher levels of the inflammatory markers CRP and IL-6, higher cortisol awakening response and higher heart rate were associated with short telomere length. Next, we found that the number of such physiological dysregulations was associated with shorter telomere length, indicating a dose-response relationship (1, 2 or 3-4 dysregulations versus no dysregulations, all p-values <.01). Overall, these findings indicate that a dysregulated physiological stress response is accompanied by shortened telomere length, although cause and effect remain to be explored.

The last study of this thesis, **Chapter 11**, examined the extent to which physiological stress systems, metabolic syndrome components and lifestyle factors explain the relationship between depressive and anxiety disorders and telomere length. Mediation analyses showed that CRP, IL-6, waist circumference, triglycerides, HDL cholesterol and cigarettes smoking were significant mediators in the relation between psychopathology and telomere length. Subsequently, when all significant mediators were included in one model, the effect sizes of the relationships between telomere length and symptom severity and current diagnosis were reduced by 36.7% and 32.7%, respectively, and the remaining direct effects were no longer statistically significant.