Psychosocial and biological aspects of dispositional optimism at old age

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Promotores:	Prof.dr.F.G. Zitman Prof. dr. R.C. van der Mast
Copromotor:	Dr. E.J. Giltay
Overige leden:	Prof. dr. P. Spinhoven Prof. dr. Gussekloo Prof. dr. Oude Voshaar (UMCG)

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Nathaly Rius-Ottenheim
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Preface

The starting point of this thesis was the finding of our group of a protective effect of dispositional optimism on all-cause and cardiovascular mortality. Although these results were interesting, the study could not disentangle through which mechanisms optimism decreased mortality risk, or whether a common third variable explained the association.

Dispositional optimism is traditionally seen as a personality trait that is rather stable over time and therefore only little changes in levels of optimism are considered possible. For this reason, we investigated optimism as both predictor and outcome in relation to different biological, lifestyle, and psychosocial factors. Until now, optimism has been mainly studied as a predictor of health, but the influences of different correlates on levels of optimism have barely been investigated. More specifically, we will examine the influences of biological (e.g. telomere length or inflammation) and lifestyle (e.g. physical activity) correlates on levels of optimism over time. In addition, we will also investigate whether levels of optimism predict psychosocial factors (e.g. loneliness) in order to confirm earlier findings. Finally, we will explore the association between optimism and mental imagery, which has been suggested as a useful tool to increase levels of optimism and may have therapeutic potential.

Thesis outline

Chapter 1 provides an overview of the research that has been done in the field of optimism and gives a context to understand the following chapters. In this chapter, the definition of dispositional optimism and its differences in relation to other related concepts are also discussed.

Chapters 2 through 4 describe the cross-sectional and prospective associations between biological factors and levels of optimism. Chapter 2 describes the association between longevity and optimism, using an inter-generational design. This approach does not only allow to confirm earlier findings of a relationship between lifespan and optimism, but also gives some directions on a potential shared heritability of longevity and optimism. In chapter 3, the association of a marker of cellular aging, telomere length, and optimism is examined. Moreover, extending the findings of earlier studies, we also examined this association longitudinally. In chapter 4, the associations between haplotypes of a marker of inflammation, C-reactive protein (CRP), and optimism are explored, taking also the potential modulating effect of obesity into account.

Chapter 5 describes the associations of physical activity with optimism and depressive symptoms. In this study we did investigate both the correlation of changes in physical activity in relation to changes in optimism or depressive symptoms and the predictive value of baseline physical inactivity on levels of optimism or depressive symptoms at the end of the follow-up. In this way, we were able to explore in detail the complex associations between physical activity and psychological well-being and also the potential beneficial effects of physical activity on optimism.

Chapter 6 describes a study that investigated the predictive effect of optimism on loneliness. Furthermore, in this study a clear distinction is made between two subtypes of loneliness: emotional and social loneliness. This distinction is particularly relevant in older samples, such as the one used here. This study sought to confirm the results of earlier studies that have found that levels of optimism influence psychosocial outcomes. Furthermore, the

association between low optimism and loneliness is of particular relevance because both factors predict poorer prognoses in these patients.

Chapter 7 portrays the cross-sectional associations between optimism and mental imagery, which is a property that is thought to be increased in optimistic persons. The elucidation of this association may provide further evidence for experimental studies that aim to develop interventions to increase optimism.

Finally, in the discussion section (chapter 8), the findings described from chapters 2 through 7 are summarized and discussed. Furthermore, methodological considerations and directions for future research will be addressed. Potential implications for public health and clinical practice will be outlined as well.

Chapter 1

The role of dispositional optimism in physical and mental well-being

Quality of Life: A Positive Psychology Perspective

Nathaly Rius-Ottenheim
Roos C van der Mast
Frans G Zitman
Erik J Giltay

Abstract

Dispositional optimism is a personality trait that refers to the extent to which individuals expect positive outcomes for their future. Higher optimism has been associated with a better physical health and mental well-being. It is thought that these favorable outcomes result from the more effective coping styles used by optimists. These coping styles include goal-oriented strategies which enhance the perception of controllability of stressors and better social embedding and protect against feelings of loneliness. Optimists meet adversities using a proactive approach to deal with the source of stress, whether it concerns a health, psychological, or social problem. Dispositional optimism has been associated with a reduced risk for various physical disorders, including a lower risk for cardiovascular disease morbidity and mortality, whereas evidence for a link with cancer is more ambiguous. The protective effect of optimism on physical health may be mediated through health-promoting behaviors, such as healthier dietary patterns and more physical activity. Biological processes such as low inflammation, low oxidative stress, and a resilient hypothalamic-pituitary adrenal axis activity may underlie the association. It is therefore undeniable that dispositional optimism plays a central role in health-related quality of life and subjective well-being. Intervention studies aiming to increase optimism are scarce and have shown that manipulation of one's future expectancies may change dispositional optimism on the short term. Future well-designed trials should therefore explore whether the level of optimism can be improved through cognitive behavior therapy, exercise, lifestyle modification, social skills training or biological interventions.

1. Introduction

In the last decades more research has focused on the beneficial effects of positive psychological factors on health. One of the most extensively investigated factors of positive psychology is optimism. It is commonly believed that being optimistic confers a buffer against mental and physical health problems. But are these benefits real? Do optimistic people fare better when facing challenges and adversity? And, if so, what are the mechanisms underlying these associations? This review aims to provide the reader with an overview of the current knowledge on optimism and its correlation with several biological and psychosocial markers.

2. Optimism

Reviewing the literature, it appears that the notion of optimism has been approached from a variety of perspectives. Basically, optimism involves holding positive expectancies for one's future. However, while some theoretical views focus on expectancies that apply to a particular situation, others focus on more general expectancies. There are two main scientific conceptualizations which are theoretically interconnected but not equivalent, i.e. dispositional optimism (Scheier *et al*., 1994) and explanatory (style) optimism (Peterson & Seligman, 1984).

Dispositional optimism refers to one's generalized positive expectations towards the future (Carver *et al*., 2010) and is usually measured by asking people directly whether they expect their future to be good or bad (Scheier *et al*., 1994). People with high dispositional optimism tend to expect good things rather than bad things to happen in their future. On the contrary, people with low dispositional optimism have the inclination to anticipate negative outcomes regarding life challenges and have the perception that these situations are unchangeable and uncontrollable. These perceptions of lack of control on a stressor are linked to learned helplessness, by which people become passive and unresponsive to the stressor because they believe that there is no sense in trying to change something that is unchangeable (Maier & Seligman, 1976). These differences in expectations on one's future are thought to greatly influence our behavior. The concept of dispositional optimism is based on the self-regulation theory of Carver and Scheier, which posits that people organize their behavior towards goals they perceive as desirable and attainable (Carver *et al*., 2010). Accordingly, individuals who hold positive expectations for their future see their desired outcomes as attainable and endeavor in the achievement of their goals. In contrast, people who hold negative expectations for their future see their desired outcomes as unattainable and give up more easily. Thus, without confidence in the attainability of the desired goals, no action will be taken to achieve them.

Explanatory optimism or an optimistic explanatory style rests on the hypothesis that future expectancies are mainly derived from attributions to past events (Peterson & Seligman, 1984). This conceptual model stems from the learned helplessness theory (Seligman, 1975). This model proposes that people with an optimistic explanatory style attribute drawbacks to temporary, external, and specific situations, whereas people with a negative explanatory style attribute problems to permanent, internal, and global causes (Gillham *et al*., 2001; Tomakowsky *et al*., 2001). Therefore, explanatory optimism is commonly assessed by measuring patterns of attributions about the causes of past events and inferring whether these past attributions ultimately yield future expectancies.

As evident from these definitions, there is a clear theoretical connection between dis-

positional optimism and explanatory style optimism; both assume that the consequences of optimism derive from differences in expectancies (Scheier & Carver, 1992). However, there are also some important differences between dispositional optimism and explanatory optimism. Whereas explanatory style optimism focuses on the attributions that people give to a certain past event, dispositional optimism directly measures one's future expectancies. Therefore, dispositional optimism centers around a focus on the future and is closely related to life engagement, vitality, and feelings of having a purpose in life (Giltay *et al*., 2006a). Furthermore, the difference between dispositional optimism and explanatory style optimism has been confirmed by the relatively poor correlations (range 0.10–0.25) found between the two scales that measure these two conceptualizations of optimism (Ahrens & Haaga, 1993; Dember, 2001; Peterson & Vaidya, 2001; Tomakowsky *et al*., 2001).

Besides these two main conceptualisations of optimism, other approaches have also been proposed. The self-efficacy theory is based on people's expectancies of being able to execute desired behaviors successfully by using adequate coping strategies across a broad range of demanding situations (Schwarzer, 1994). In contrast to dispositional optimism, the self-efficacy theory is more focused on the importance of personal agency in subsequent behavior and holds that this behavior is best predicted by domain-specific expectancies (Bandura, 1982).

Another way to look at optimism is unrealistic optimism, which is characterized by people's tendency to overestimate the chances of future desirable outcomes (Helweg-Larsen & Shepperd, 2001; Weinstein, 1980; Weinstein & Klein, 1996). People may consider their chances of getting happily married or receiving a promotion above average (Lench, 2009). There is some evidence that the general population is prone to be overly (and unrealistically) optimistic (Klein & Weinstein, 1997). However, there are cultural and gender differences. It seems that people from Western cultures (i.e. North America, Western Europe) are more likely to be unrealistically optimistic than people from Eastern cultures (i.e. Japan), when comparing their risk perception of potential adverse future events (Rose *et al*., 2008). Furthermore, men are more likely to be overconfident about their chances to avert a negative event than women (Lin & Raghubir, 2005).

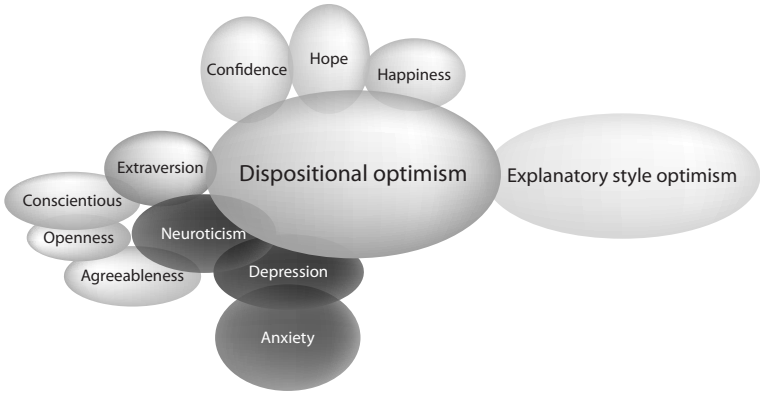

Figure 1. Psychological constructs related to dispositional optimism.

Other constructs related to optimism are hope, hopelessness and happiness. Optimism has been inversely related to hopelessness, which refers to the incapacity to imagine plausible ways to achieve a personal goal (Snijder *et al.*, 2002). Compared to hope, dispositional optimism may reflect more general beliefs about a variety of aspects (Rand, 2009). Thus, hope focuses more directly on the personal attainment of specific goals, whereas optimism focuses more broadly on the expected quality of future outcomes in general (Bryant & Cvengros, 2004). Nevertheless, optimism has been shown to be significantly correlated with hope (r=0.55) (Magaletta & Oliver, 1999). Happiness is a state that reflects a positive balance when a person evaluates positive versus negative experiences and perceives that this balance has met his/her expectations (Veenhoven, 1994). Dispositional optimism, by contrast, is a personality trait that implies a disposition to believe that, in our future, good things are more likely to happen than bad things (Scheier *et al.*, 1994). Optimism and happiness are interrelated, but happiness is less stable over long periods of time and is more closely linked to hedonism and more dependent on environmental factors, such as economic and social problems (Veenhoven, 2003).

In the following sections, we give an overview of important determinants of optimism, the effects of optimism on health outcomes, and the potential mechanisms underlying these associations. In view of the fact that our group has primarily investigated dispositional optimism, the current literature review will only focus on studies concerning dispositional optimism and its correlates with health outcomes, coping, biological factors, and social integration. Thus, throughout this chapter, when we refer to optimism, we explicitly refer to dispositional optimism.

3. Development of optimism

Optimism is thought to stem from a combination of genetic and environmental factors (Gillham & Reivich, 2004; Vaughan, 2000). Although there is some indication of a genetic predisposition for optimism, it does not explain how optimism develops (Plomin *et al.*, 1992). Increasing evidence suggests that also certain environmental factors during childhood may play a crucial role in the development of one's disposition to optimism (Gillham & Reivich, 2004). For example, children who experience negative events in childhood, such as abuse or parental hostility, are more likely to display lower optimism (Brodhagen & Wise, 2008; Hjelle *et al.*, 1996; Korkeila *et al.*, 2004). Furthermore, parents appear to be able to increase the optimistic outlook of their children by modeling their children's optimistic beliefs and behaviors when facing adversity. Parents may also promote optimism by helping their children build skills and develop beliefs in their ability to face challenges (Gillham & Reivich, 2004). Also a secure attachment between parents and their children appears to increase levels of optimism of the children (Carver & Scheier, 2002). Other predictors of higher levels in optimism in the adolescence and early adulthood are parental socioeconomic status, school achievement, vocational education, and work history (Ek *et al.*, 2004). Younger age has been found to be predictive of higher levels of optimism, also in older populations (Giltay *et al.*, 2006a). Other correlates of higher levels of optimism in older age are a higher education, living with others, and feeling healthy (Giltay *et al.*, 2007a). However, it is yet to be investigated whether these or other sociodemographic factors may predict higher levels of optimism over time in older adults.

4. Measuring optimism

The most commonly used instrument to measure dispositional optimism is the Life Orientation Test (LOT), which was developed by Scheier and Carver in 1985. This instrument was later revised (becoming a briefer version) to eliminate some content overlap with coping and to exclude items that did not completely refer to positive expectations (Scheier *et al*., 1994). This newer version was called the Life Orientation Test-Revised (LOT-R) and consists of 10 items rated on a 5-point Likert scale, with six items yielding an optimism score and four filler items (Figure 1) (Scheier *et al*., 1994). Scheier and Carver (1985) reported a Cronbach's alpha of .76 and a test-retest correlation of .79 over a 4-week period. In a later psychometric analysis of the LOT-R a Cronbach's alpha of .71 was reported (Herzberg *et al*., 2006). Other instruments to measure optimism include the four-item questionnaire (4Q) and a subscale of the Scale for Subjective Wellbeing of Older subjects (SSWO). The 4Q consists of four statements rated on a 3-point Likert scale (Figure 2)(Giltay *et al*., 2006b). A Cronbach's alpha of .71 was reported for the 4Q (Giltay *et al*., 2008). The SSWO optimism subscale consists of seven items also rated on a 3-point Likert scale (Giltay *et al*., 2004) (Figure 3). A Cronbach's alpha of .76 has been reported for the optimism subscale of the SSWO (Giltay *et al*., 2004).

An issue that frequently arises in optimism research is the dimensionality of the most frequently used LOT-R. While some studies support the use of the LOT-R as a uni-dimensional scale (optimism) (Achat *et al*., 2000; Scheier *et al*., 1999; Segerstrom *et al*., 1998), others support a bidimensional approach (optimism and pessimism) (Herzberg *et al*., 2006; Kubzansky *et al*., 2004; Mroczek *et al*., 1993). Segerstrom *et al*. found that the LOT-R was best used as a unidimensional scale, but recognized that there is some psychometric evidence for bidimensionality (Segerstrom *et al*., 2011).

5. Temporal stability of optimism

Dispositional optimism has been posited as a trait-like characteristic that determines the self-regulation of behavior (Scheier & Carver, 1992). A reliability coefficient of the LOT ranging from .58 to .82 has been reported over periods of time lasting from several weeks to one year (Atienza *et al*., 2004; Scheier *et al*., 1994). Similar reliability coefficients (Cronbach's alpha of 0.78) were found for the 4Q in a prospective study with 15-years of follow-up (Giltay *et al*., 2006b). Thus, one's level of optimism is presumably relatively stable over time, as is also evident from the high temporal stability in longitudinal studies (Achat *et al*., 2000; Bromberger & Matthews, 1996; Scheier *et al*., 1994). In a small non-randomized study, dispositional optimism remained relatively unaffected after intensive mental training and physical coaching (Norlander *et al*., 2002). However, fluctuations in optimism over time have also been reported, suggesting that changes in dispositional optimism are possible (Sweeney *et al*., 2006).

6. Optimism as a predictor of health outcomes

Epidemiological studies have shown that degree of optimism is related to a myriad of health outcomes, both in the general population and in patients. Higher levels of optimism correlate with subjective health outcomes such as a perceived health or better functional status (Achat *et al*., 2000) and objective health measures such as disease progression and mortality (Chida & Steptoe, 2008). Especially cardiovascular mortality risk and survival have been well-investigated (Giltay *et al*., 2004; Giltay *et al*., 2006a). Regarding mental health, optimism has

been associated with better psychological well-being (Cederblad *et al*., 1995; Giltay *et al*., 2006b), less depressive symptoms (Giltay *et al*., 2006b), and better psychological adjustment in chronically ill patients (Fournier *et al*., 2002a). In the following sections, we provide an overview of the different correlations between optimism and physical and mental health.

6.1 Physical health

6.1.1 Physical functioning and perceived health

In the last decades, optimism has been increasingly associated with better health outcomes and quality of life (Bain *et al*., 2003; Wrosch & Scheier, 2003). An analysis of the Normative Ageing Study showed that dispositional optimism was positively correlated with several scales of the Medical Outcome Study 36-item short-form health survey (SF-36), independently of depression and demographic variables in middle-aged men (Achat *et al*., 2000). Similarly, another study among older women showed that optimism was associated with better physical functioning (Umstattd *et al*., 2007). Self-rated health was also strongly associated with levels of optimism in community-dwelling older persons (Giltay *et al*., 2007a). This association has also been found in patient populations. A study among patients receiving cardiac rehabilitation showed that higher optimism was positively associated with perceived health through more adaptive coping (Shen *et al*., 2004).

6.1.2 Morbidity and mortality

6.1.2.1 Cardiovascular disease

There is increasing evidence suggesting that optimism may also affect disease progression and recovery (Table 1). Scheier *et al* studied the effects of optimism in a group of patients undergoing coronary artery bypass surgery and found that those patients with higher optimism scores responded better to the surgical intervention and displayed a faster physical recovery (Scheier *et al*., 1999). These beneficial effects were also present six months after the intervention, as optimistic patients were more likely to engage in vigorous physical exercise and resume work (Scheier *et al*., 1989). In a similar study conducted among women who underwent a coronary artery bypass operation, women who were optimistic were more likely to accept their situation and to display more favorable outcomes (King *et al*., 1998). In a later longitudinal study among patients participating in a cardiac rehabilitation program, optimism was found to decrease global coronary risk by increased aerobic capacity through engagement in healthy behaviors (Shepperd *et al*., 1996). Accordingly, a prospective study among patients undergoing a cardiac transplantation showed that positive expectations predicted better adherence to medical treatment and a favorable recovery (Leedham *et al*., 1995).

Optimism has also been associated with survival and decreased mortality risk both in community-dwelling healthy populations and in patients (Chida & Steptoe, 2008). In a prospective study among a community-dwelling population of elderly men and women, higher optimism scores were predictive for less all-cause and cardiovascular mortality after 9 years of follow-up, although this association was stronger in men than in women (Giltay *et al*., 2004). These findings were confirmed in a later study which specifically investigated the risk of cardiovascular death in a cohort of older men from the general population (Giltay *et al*., 2006a). The latter study showed that the association with all-cause mortality was substantially weaker (Giltay *et al*., 2006c).

6.1.2.2 Cancer

The evidence of optimism being beneficial for disease progression and recovery in patients

with cancer is less consistent. A study among post-operative breast cancer patients showed that optimism was associated with less altered immune responses as, for example, less natural killer cell activity (Von Ah *et al.*, 2007). Furthermore, higher optimism scores were associated with better physical functioning and less somatic complaints in patients with cancer (Tallman *et al.*, 2007; Wyatt *et al.*, 1999).

The association between optimism and cancer mortality has been examined in cohorts of cancer patients, but with mixed results. While some prospective studies found a protective effect of dispositional optimism on survival of cancer patients (Allison *et al.*, 2003; Butow *et al.*, 1999; Schulz *et al.*, 1996), others did not (Schofield *et al.*, 2004). However, as reported in a review on the relationship between coping styles and cancer survival, studies displaying positive findings were mostly small, with short follow-up periods, and lacked adjustment for important confounders (Petticrew *et al.*, 2002). In more recent and larger prospective studies no evidence was found for lower survival rates in cancer patients with higher optimism levels prior to treatment (Schofield *et al.*, 2004). In a study among community-dwelling older men, optimism did not predict a lower risk of non-cardiovascular mortality, especially cancer mortality (Giltay *et al.*, 2006c). Taken together, there is little and inconsistent evidence that a higher level of dispositional optimism helps to increase survival rates in cancer patients.

6.1.2.3 Chronic diseases

The benefits of optimism have also been studied in relation to chronic diseases. In a longitudinal study among patients with diabetes mellitus low optimism was identified as a risk factor for worsening levels of glycosylated hemoglobin after one year of follow-up (Yi *et al.*, 2008). Furthermore, optimism was also reported to predict less somatic complaints in patients with diabetes mellitus (Motivala *et al.*, 1999). Further research showed that optimism was related to slower disease progression in patients with human immunodeficiency virus (HIV) (Ironson *et al.*, 2005; Ironson & Hayward, 2008; Milam *et al.*, 2004), patients with arthritis (Ferreira & Sherman, 2007; Fournier *et al.*, 2002b), patients undergoing hemodialysis (Morales Garcia *et al.*, 2011), and patients with obstructive pulmonary diseases (Kubzansky *et al.*, 2002). Dispositional optimism was also related to better adjustment to certain diseases, such as Parkinson's disease or multiple sclerosis (Ridder *et al.*, 2000). Nevertheless, these studies provided only correlational evidence and cannot imply causation since residual confounding and reverse causation may play an important role in these relationships. In other words, it is possible that chronic diseases with an aggressive progression may result in poorer levels of optimism than chronic diseases with milder progression.

6.2 Mental well-being

Dispositional optimism has been related to a greater stress resilience and lower risk for mental health problems, such as depressive or anxiety symptoms (Scheier *et al.*, 1994). Several studies have reported more depressive symptoms in young or middle-aged adults with lower optimism (Bromberger & Matthews, 1996; Cohen *et al.*, 2001; Fontaine & Jones, 1997; Shnek *et al.*, 2001). A prospective cohort study with 10 years of follow-up among college students showed that high optimism was predictive of less depressive symptoms at the end of the follow-up, even after adjustment for baseline depressive symptoms, negative affect, positive affect, and daily hassles (Vickers & Vogeltanz, 2000). Furthermore, there is also some evidence to suggest that optimism buffers the relationship between hopelessness and suicidal ideation in depressed young adults (Hirsch & Conner, 2006). In middle-aged adults, optimism was found to be predictive of less depressive symptoms (Andersson, 1996), reduced

duration of the depressive episode and the time till the patient resumed work (Kronstrom *et al*., 2011). Those few studies among older persons have also shown an inverse association between optimism and depression (Isaacowitz & Seligman, 2002). In a prospective cohort study among elderly men, a lower cumulative incidence of depressive symptoms was found among those men with higher optimism scores (Giltay *et al*., 2006b). Accordingly, in another study among community-dwelling older women, low optimism was found to be associated with sub-threshold depression (Vahia *et al*., 2010). A recent prospective study among middle-aged depressed participants showed that persons with higher optimism scores displayed a better and faster recovery without the need of a lengthy treatment as less optimistic persons (Karlsson *et al*., 2011). Thus, even after development of a depressive episode, dispositional optimism seems to have a beneficial effect on the recovery process. The association of optimism with depressive and anxiety has also been found among cancer patients (Horney *et al*., 2011; Zenger *et al*., 2010). All in all, dispositional optimism seems to have a beneficial effect on the recovery process even after the development of a depressive episode.

7. Potential mechanistic correlates of optimism

From the reviewed literature, it is clear that dispositional optimism is positively associated with a wide range of positive health outcomes, regarding both mental and physical health. Nonetheless, most studies only provide evidence of a correlation and cannot unequivocally answer the question of causation. Despite this uncertainty, a number of potential psychosocial and biological mechanisms have been proposed to explain the associations between dispositional optimism and favorable health outcomes. This section presents a summary of the literature on these potential underlying mechanisms.

7.1 Coping style

The protective effect of optimism on health is thought to be partially explained by optimists' engagement in more adaptive coping strategies in the face of uncontrollable stressors such as a health disorder (Taylor, 2007). Coping refers to the cognitive and behavioral adaptation to manage demands that exceed the resources of a person (Lazarus & Folkman, 1984). Since coping involves the interaction between the person and his/her environment, it is reasonable to expect variation among people in their predispositions to cope in particular ways (Nes & Segerstrom, 2006).

Coping is commonly thought to be a mechanism through which dispositional optimism translates into better adjustment to stressors (Aspinwall & Taylor, 1992; Park *et al*., 1997; Scheier & Carver, 1985). Optimism is positively associated with approach-oriented coping (e.g. positive reappraisal and acceptance) and inversely associated with avoidance coping (e.g. denial and behavioral disengagement). Approach-oriented coping refers to the engagement of cognitive and behavioral efforts to reduce, eliminate, and actively manage the demands evoked by a stressor (Suls & Fletcher, 1985). This mediation is explained in the behavioral self-regulation model proposed by Carver and Scheier (Carver & Scheier, 2000). In this model, when a desired goal is blocked (e.g., due to a threat or challenge), optimists put forth more effort on overcoming the obstacle because of their conviction that positive outcomes are attainable. Presumably, approach-oriented coping is more likely to be used in situations that are perceived as amenable to positive change. Furthermore, as shown in a meta-analysis on the association between optimism and coping, optimists show active attempts to change and accommodate to stressors, reflecting flexible engagement in adaptive coping regarding

TABLE 1. Studies investigating the associations of dispositional optimism with somatic morbidity and mortality

Study	N	Sample type	Optimism measure	Outcome	Study design	Results
Review studies:						
Chida et al (2008)	70 studies	Healthy & disease populations	Several scales	Survival	Meta-analysis of longitudinal studies	Optimism predicted survival
Ironson et al (2008)*	122 studies	HIV patients	Several scales	Disease progression	Review of longitudinal studies	Optimism predicted slower disease progression
Original research:						
Allison et al (2003)	101	Patients with head and neck cancer	LOT	Survival	Longitudinal, FU= 1 year	Optimism predicted survival
Butow et al (1999)	125	Patients with metastasic melanoma	COPE	Survival	Longitudinal, FU= 2 years	Optimism predicted survival
Ferreira et al (2007)	73	Patients with osteoarthritis	LOT-R	Well-being	Cross-sectional	Optimism associated to less pain and higher well-being
Fournier et al (2002b)	104	Patients with chronic diseases	LOT-R	Physical functioning (SF-36)	Cross-sectional	Optimism associated with better adaptation to disease
Giltay et al (2004)	941	Older community-dwelling subjects	SSWO	All-cause and CV mortality	Longitudinal, FU= 9 years	Optimism predicted less all-cause and CV mortality
Giltay et al (2006b)	887	Older community-dwelling men	4-item questionnaire	CV mortality	Longitudinal, FU= 15 years	Optimism predicted less CV mortality
Ironson et al (2005)	177	HIV patients	LOT-R	Disease progression	Longitudinal, FU= 2.5 years	Optimism predicted slower disease progression
King et al (1998)	55	Women undergoing by-pass surgery	LOT	Sickness impact profile	Longitudinal, FU= 12 months	Optimism predicted better functional ability
Milam et al (2004)	412	HIV patients	LOT-R	Disease progression, CD4 counts	Longitudinal, FU= 18 months	Moderate optimism predicts less disease progression
Morales García et al (2011)	239	Patients undergoing chronic haemodialysis	LOT-R	Health related quality of life	Cross-sectional	Optimists associated with subjective health status
Motivala et al (1999)	38	Diabetic patients	LOT	Somatic complaints	Longitudinal, FU= 10 years	Optimism predicted less somatic complaints
Ridder et al (2000)	166	PD or MS patients	LOT	Adaptation to disease	Cross-sectional	Optimists associated with better adaptation to disease
Shepperd et al (1996)	22	Cardiac patients	LOT	Global Coronary Risk	Longitudinal, FU= 18 weeks	Optimism predicted less CV morbidity
Scheier et al (1989)	51	Middle-aged men	LOT	Physical function after operation	Longitudinal, FU= 6 months	Optimism predicted better recovery
Scheier et al (1999)	309	Patients undergoing by-pass surgery	LOT-R	Rehospitalization rate	Longitudinal, FU= 6 months	Optimism predicted lower rehospitalization rates
Schofield et al (2004)	204	Patients with lung cancer	LOT	Survival	Longitudinal, FU= 5 years	Optimism did not predict lung cancer survival
Schulz et al (1996)	238	Cancer patients	LOT	Mortality	Longitudinal, FU= 8 months	Low optimism predicted mortality
Tallman et al (2007)	56	Cancer patients	LOT	Positive coping	Longitudinal, FU= 3 years	Optimism predicted better coping
Tomakowsky et al (2001)	78	HIV-infected men	LOT, EASQ	CD4 counts	Longitudinal, FU= 2 years	Optimism did not predict CD4 counts
Von Ah et al (2007)	54	Breast cancer patients	LOT-R	Immunological markers	Cross-sectional	Optimism was not associated with immune responses
Wyatt et al (1999)	699	Cancer patients	LOT	Somatic complaints	Longitudinal, FU= 6 weeks	Optimism predicted less somatic complaints
Yi et al (2008)	111	Diabetes patients	LOT	Glycosylated hemoglobin	Longitudinal, FU= 1 year	Low optimism predicted worsening HbA1c

COPE= General Coping Strategies Scale; CV= cardiovascular; EASQ= Expanded Attribution Style Questionnaire; FEV1= Forced Expiratory Volume in 1 second; FVC= Forced Vital Capacity; FU= follow-up; HbA1c= glycosylated hemoglobin; HIV= Human Immunodeficiency Virus-infection; LOT= Life Orientation Test; LOT-R= Life Orientation Test- Revised; MMPI-2= Minnesota multiphasic personality inventory-2; MS= Multiple Sclerosis; PD= Parkinson's disease; SF-36= short form 36 health survey questionnaire; SSWO= Dutch Scale of Subjective Well-being for Older Persons.

controllability of stressors (Nes & Segerstrom, 2006). In this meta-analysis, larger effect sizes were found for approach coping in relation to academic and health stressors, whereas emotion-approach coping was more strongly associated with traumas. In other words, even when the stressor is uncontrollable or unchangeable (e.g. traumatic events), optimists use a coping strategy that seeks to reduce or manage the emotional consequences of the stressor.

Thus, in summary, optimists tend to view a stressful situation in a more positive light, develop a problem-focused strategy to face the stressor, and are more flexible regarding the demands of the stressor (Scheier *et al*., 1994).

7.2 Social integration

Optimism also seems to play an important role in the social domain, as evident from an increasing amount of research in this field. Although little is known about the potential protective effect of optimism on loneliness, several cross-sectional studies have shown that optimism is linked to less loneliness in college students (Montgomery *et al*., 2003; Neto & Barros, 2003) and in low-vision older women (Barron *et al*., 1992). This association has also been investigated in several longitudinal studies (Brissette *et al*., 2002; Jackson *et al*., 2000; Nurmi *et al*., 1996; Rius-Ottenheim *et al*., 2011; Srivastava *et al*., 2006). One longitudinal study examined the effect of dispositional optimism and quality of close relationships on loneliness in a college student sample during a 6-week follow-up period and showed that lower levels of optimism and social support were associated with more feelings of loneliness (Jackson *et al*., 2000). In another longitudinal study among college students, higher optimism was prospectively associated with greater increases in perceived social support over 6 months of follow-up (Brissette *et al*., 2002). Accordingly, results from a longitudinal study among college students study indicated that less optimistic students were more likely to use a social-avoidance coping strategy and felt more loneliness than their more optimistic peers (Nurmi *et al*., 1996).

Optimism is also beneficial for social integration in older populations. A study among older married couples showed that optimism was predictive of a better relationship status after one year of follow-up (Srivastava *et al*., 2006). Another prospective study among community-dwelling older men showed that higher optimism scores were predictive of lower loneliness scores after 10 years of follow-up (Rius-Ottenheim *et al*., 2011). It is conceivable that, after a negative event, optimists use coping strategies that foster more positive appraisals of the existing social network or lead to actively pursue new social relationships (Scheier *et al*., 1986). In this way, dispositional optimism might lead to the achievement of a better social embedding and protect against feelings of loneliness.

7.3 Health behaviors

Another pathway through which optimism may influence health is through engagement in health promoting behaviors and avoidance of health damaging behaviors (Giltay *et al*., 2007a). This hypothesis has been confirmed by linking dispositional optimism to non-smoking, increased physical activity, moderate alcohol use and consumption of more fruits, vegetables, and whole grains (Giltay *et al*., 2007b; Kelloniemi *et al*., 2005; Steptoe *et al*., 2006). The engagement in more healthy behaviors is, in turn, critical for prevention of chronic conditions such as cardiovascular diseases or metabolic syndrome (Blokstra *et al*., 2010; Yamashiro *et al*., 2010).

Physical activity has frequently been proposed as a lifestyle factor that might mediate the association between positive psychological factors and better health outcomes. Optimism is

cross-sectionally associated with physical activity (Giltay *et al*., 2007b; Kavussanu & McAuley, 1995). However, more studies with a prospective design are needed to elucidate the direction of causality of this association.

Optimism has been inversely associated with smoking dependence and alcohol use. Two cross-sectional studies among twin females (Kendler *et al*., 1999) and school students (Carvajal *et al*., 2000); and another prospective study among college students (Baker, 2007) have shown that persons with higher optimism scores are less likely to develop nicotine dependence. Regarding alcohol use, cross-sectional evidence has associated higher optimism with moderate alcohol use (Steptoe *et al*., 2006), while lower optimism has been associated with heavy alcohol consumption (Kelloniemi *et al*., 2005). Accordingly, a prospective study among community-dwelling older men showed that higher optimism was predictive of moderate alcohol consumption (Giltay *et al*., 2007b). Thus, there seems to be a non-linear U-shaped association between alcohol use and optimism.

Optimists are more likely to have healthier dietary habits, as they tend to consume more foods rich in fiber and low in fat or saturated fats. A Finnish cross-sectional study showed that higher optimism scores were positively associated with higher consumption of fresh vegetables or salads, berries, fruit, low-fat cheese, and salad dressing (Kelloniemi *et al*., 2005). Another cross-sectional study among a Dutch older population showed that optimists were more likely to consume more fruit, vegetables, whole-grain bread, and fish fatty acids (eicosapentanoic acid [EPA] and docosahexaenoic acid [DHA]; however with borderline significance) (Giltay *et al*., 2007b). These cross-sectional findings regarding fish fatty acids were only partially confirmed in a later longitudinal study among older community-dwelling men and women, as the consumption of fish fatty acids was associated with optimism measured with the 4Q, but not with the LOT-R (van de Rest *et al*., 2010).

Some have argued that health-related behaviors might be seen as coping strategies used in contexts in which the source of stress is health-related (i.e. due to an illness or physical disability). That is, as being in good health is a desired goal, optimists tend to engage in positive health practices to achieve their goal. In this way, health-promoting behaviors are presumably related to optimists' capacity to anticipate benefits of behavioral change on health (Aspinwall & Brunhart, 1996). This hypothesis has been confirmed in both patients and population-based studies. In a study among patients following a cardiac rehabilitation program it was observed that patients with higher optimism scores achieved a greater success in lowering levels of saturated fat, body fat, and global coronary risk by embracing a healthier diet and raising the level of physical exercise across the rehabilitation period (Shepperd *et al*., 1996). Also in another study among chronically ill patients, it was found that higher optimism predicted greater engagement in self-care behaviors (de Ridder *et al*., 2004). Finally, in a group of undergraduate students it was shown that dispositional optimism was positively correlated with engagement in health-promoting behaviors (Robbins *et al*., 1991).

7.4 Systemic stress, oxidative stress, and inflammation

The association between dispositional optimism and better physical health is probably not exclusively mediated by lifestyle factors, but also through biological factors.

Chronic stress is associated with impaired immunity and increased inflammatory markers (Kemeny & Schedlowski, 2007). Several studies have aimed to elucidate the moderating

effect of optimism on the relationship between stress and immunity. A study among college students under stress, found that those students with lower optimism scores displayed an increased lymphocyte turnover and an improved natural killer cell activity when compared with students with lower optimism scores (Segerstrom, 2001). More recently, the same authors showed that changes in optimism were correlated to changes in cell-mediated immunity, although this association was partly mediated by positive affect (Segerstrom & Sephton, 2010). Similarly, a prospective cohort study found an association between higher optimism and T lymphocytes (CD8+, CD11b+), but only in case of acute stressors and not with prolonged stressors (Cohen *et al.*, 1999). In older persons, optimism has also been associated with a better immune response to influenza vaccine (Kohut *et al.*, 2002).

It has been hypothesized that changes in immune responses may result from the effects of psychological stress on the activation of the hypothalamic-pituitary-adrenal (HPA) axis. Psychological stress enhances release of glucocorticoids which are, in turn, responsible for changes in cellular and humoral responses (Glaser & Kiecolt-Glaser, 2005). The resultant release of glucocorticoids may also affect the systemic inflammatory status. In a study among middle-aged healthy adults (n=6814), higher dispositional optimism scores were inversely associated with circulating levels of C-reactive protein (CRP), a non-specific systemic inflammatory acute-phase protein (Roy *et al.*, 2010). Another study using a Mendelian randomisation design, haplotypes of the CRP (a well-known inflammatory marker) were found to be associated with dispositional optimism, but only in the overweight/obese group (BMI >25 kg/m2) (Rius-Ottenheim, 2011a). This finding suggests that the association between dispositional optimism and inflammation levels may be moderated through longstanding changes in health behaviours and lifestyle.

On the cellular level, telomere length has become increasingly popular in the study of the effects of chronic stress on the immune system (e.g. leukocytes). Telomeres are repetitive DNA sequences that cap chromosomal ends and play a critical role in promoting chromosomal stability (Blackburn, 2001). When the telomeres reach a critical minimal length, the cell will go into senescence, leading ultimately to apoptosis. Since telomere length reflects the number of cell divisions, it has been proposed as a marker of biological aging. Telomeres shorten more rapidly under certain conditions, such as exposure to prolonged stressors (e.g. oxidative stress) (Richter & Von Zglinicki, 2007). Therefore, it has been hypothesized that chronic psychological stress may be translated in accelerated telomere attrition. Several cross-sectional studies among middle-aged adults have documented telomere shortening in relation to dispositional pessimism (O'Donovan *et al.*, 2009). However, in a prospective study investigating the association between leukocyte telomere length and dispositional optimism, no association was found between changes in telomere length and changes in dispositional optimism (Rius-Ottenheim, 2011b).

8. Interventions to increase optimism

To date, very little experimental work has been conducted to examine interventions to increase optimism and, if present, was mainly focused on explanatory optimism (Gillham & Reivich, 2004; Ruthig *et al.*, 2004). Only recently, more studies have focused on interventions to (temporarily) increase dispositional optimism by means of experimental manipulation. Findings from these recent experimental studies indicate that an individual's future expectancies are malleable and may result in increased levels of dispositional optimism (Fosnaugh *et al.*, 2009; Peters *et al.*, 2010). The first study was conducted among 160 college

students who took part in two different experiments to increase optimism: one based on positive mental imagery and the other based on optimism priming. In both experiments, after a follow-up of a couple of weeks, students who had participated in the interventions displayed higher optimistic responses than those students in the control condition (Fosnaugh *et al.*, 2009). Similar results were reported in a second intervention study in which 82 college students were asked to imagine their best possible self using mental imagery and found that the intervention of mental imagery increased dispositional optimism levels, independently of mood changes during the intervention (Peters *et al.*, 2010). Extending these findings, a recent experimental study among 54 college students showed that positive imagery increased optimism independently of mood and that the achieved changes in optimism were sustainable over the limited time period of two weeks (Meevissen *et al.*, 2011). Although these studies provide preliminary evidence on the potential of a facet of cognitive behavioural therapy (CBT) (i.e. mental imagery) to increase dispositional optimism, some issues may hamper the interpretation of their results, such as the short follow-up periods. Furthermore, all these studies were conducted among young healthy participants and, given the correlates of dispositional optimism with health, it would be interesting to investigate the effects of CBT in a sample of older participants, patients with a somatic disease, and in patients with current or lifetime psychopathology.

Besides CBT other non-psychotherapeutic interventions might affect one's level of optimism. The prospective studies reviewed in the earlier sections suggest several promising avenues. First, optimism was inversely associated with depression and probably also with other forms of psychopathology (Bromberger & Matthews, 1996; Cohen *et al.*, 2001; Fontaine & Jones, 1997). Persons with very low levels of optimism should therefore be screened for major depression and (in serious cases) be referred for treatment. Second, consistent associations were found between optimism, better perceived social support, and low levels of loneliness (Brissette *et al.*, 2002; Nurmi *et al.*, 1996). This suggests that psychosocial interventions aimed at improving interpersonal relationships may be beneficial, such as social (e.g., family) support groups and social skills training (Kühner, 2000). Experimental studies should explore whether improving emotional support and social activities also improve optimism. Third, healthier diets, more physical activity, and non-obesity were associated with higher levels of optimism. It may be hypothesized that a healthier lifestyle beneficially affects one's level of optimism, which should be explored in future studies. For example, a large double-blind, randomized trial that investigated whether long-term treatment with low doses of n-3 fatty acids increase the level of optimism in over 4000 patients who had had a myocardial infarction (Kromhout *et al.*, 2010). Fourth, there is a strong association between prevalent coronary heart disease (CHD) and low optimism. This suggests that the classic risk factors for CHD such as obesity cigarette smoking, hypertension, hypercholesterolemia, and diabetes mellitus, may also be associated with optimism. Also weight loss, achieved through diet and lifestyle modification, are associated with a reduction of depressive symptoms (de Wit *et al.*, 2010). Although CHD risk factors were not directly associated with optimism (Giltay *et al.*, 2008), they may indirectly decrease optimism through the increased risk of onset of symptomatic cardiovascular disease. Future trials should explore whether treatment of high blood pressure, lipidemia, heart disease, and diabetes, may also increase levels of optimism. Such interventions (combined with smoking cessation) may also reduce chronic low-grade inflammation, which is also associated with low optimism (Rius-Ottenheim, 2011a). Fifth, more adaptive coping strategies have been associated with higher levels of optimism (Aspinwall & Taylor, 1992; Park *et al.*, 1997; Scheier & Carver, 1985). Interventional studies

show that it is possible to learn more positive coping skills in order to reduce perceived stress and depressive symptoms (Kim *et al.*, 2011). Another study in which general practitioners taught their patients more adaptive coping strategies showed improvements in affect, better management of illness, and a better quality of life (Mjaaland & Finset, 2009). Other interventions that have proven effective in the management of perceived stress include relaxation techniques, mindfulness, and guided mental imagery (Palmer & Rodger, 2009; Shapiro *et al.*, 1998). However, though mindfulness is seen as an instrument for self-regulation, there is no evidence that mindfulness may improve optimism. Presumably, the most effective way to increase one's optimism is to combine some of the above-mentioned techniques. A combined therapy called cognitive behavioral stress management (CBSM) has been used successfully in anxiety reduction. CBSM combines relaxation, guided mental imagery, deep breathing and meditation, with cognitive behavioral techniques such as cognitive restructuring, coping skills training, and interpersonal skills learning (Antoni, 2003). In a 10-week intervention study using CBSM in women with breast cancer it was shown that this combined intervention not only reduced anxiety or depressive symptoms, but also increased levels of optimism. Importantly, these effects remained 12 months later (Antoni *et al.*, 2006).

To summarise, future intervention studies are necessary and should use a longer follow-up period and investigate whether the increases of dispositional optimism are durable. Furthermore, other interventions besides CBT should be explored, particularly in older patients.

9. Concluding remarks and recommendations

From the literature reviewed here, it can be concluded that optimism is a disposition with personality trait-like characteristics that is strongly correlated to physical and mental well-being. Highly optimistic persons rate their health more positively and are at lower risk for cardiovascular disease than less optimistic persons. However, it remains unclear whether these health advantages translate into lower morbidity and mortality rates. Optimists enjoy a better mental health, as observed from the lower incidence of depressive and anxiety symptoms. Even if they actually develop depressive symptoms, optimists display a faster and better recovery than less optimistic depressed patients. This evidence emphasizes the importance of assessing the levels of dispositional optimism in healthy individuals as well as in patients. Patients with low optimism should receive more attention from health practitioners, since low levels of optimism are a risk marker for negative somatic and psychological health outcomes.

Despite the increasing evidence for a beneficial effect of dispositional optimism on health, it remains to be elucidated which mechanisms actually mediate these associations, as most evidence is derived from correlational studies. The strongest correlate of dispositional optimism may be the more effective coping. By using more adaptive, problem-oriented coping strategies, optimists adapt their behavior and are more successful in the management of adverse life events. These advantages are also translated to the social domain, as shown by several studies reporting that optimists feel less lonely and perceive more social support. The benefits of optimism on health are also related to the engagement in a healthier lifestyle. Optimists are usually more physically active, follow a healthier diet, and smoke less often than less optimistic people. An increasing amount of cross-sectional studies corroborate these relationships, which may in turn explain the lower cardiovascular risk observed in high optimistic persons. Nevertheless, the exact pathways remain to be elucidated. In fact, the nature of these associations between optimism and health is likely bidirectional. It is true that optimistic people tend to be more socially integrated and to engage and maintain healthy

behaviours; but their lifestyle probably also reinforces their optimism. In other words, it is possible that perceived social support and engagement in healthy practices, such as a change to a healthier diet, more physical activity, or weight loss, may result in increases in levels of optimism. Future longitudinal research should therefore investigate both directions of these associations between optimism, social support, and lifestyle factors.

It remains controversial whether it is possible to increase one's optimism and thereby decrease the health risks of less optimistic people. Although there is some evidence of success in the short-term manipulation of one's future expectancies, it remains unknown whether it is possible to lastingly change dispositional optimism. One could argue that in order to achieve a more enduring effect, an intervention should be aimed at experiencing actual positive outcomes instead of only imagining a positive future scenario. Alternatively, it is possible that dispositional optimism cannot be learned and that only small changes are possible in an otherwise relatively stable personality trait. Nevertheless, more reserach is necessary to prove or refute the hypothesis that having an optimistic disposition causes the prevention of or improves the recovery from physical disease.

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Appendix

The revisted life orientation test (LOT-R)

Please be as honest and accurate as you can throughout. Try not to let your response to one statement influence your responses to other statements. There are no 'correct' or 'incorrect' answers.
Answer according to your own feelings, rather then how you think 'most people' would answere.

	Strongly disagree	Disagree	Neither agree nor disagree	Agree	Strongly agree
1. In uncertain times, I usually expect the best	0	1	2	3	4
2. It's easy for me to relax	○	○	○	○	○
3. If something can go for me, it will	4	3	2	1	0
4. I'm always optimistic about my future	0	1	2	3	4
5. I enjoy my friends a lot	○	○	○	○	○
6. It's important for me to keep busy	○	○	○	○	○
7. I hardly ever expect things to go my way	4	3	2	1	0
8. I don't get upset too easily	○	○	○	○	○
9. I rarely count on good things happening to me	4	3	2	1	0
10. Overall, I expect more good things	0	1	2	3	4

Note:
Of the six items that are scored, tree are keyed in a positive direction and tree in a negative direction. Negatively worded items (i.e. items 3, 7 and 9) are reversely coded before scoring. The total score ranges from 0 to 24, and higher scores indicate greater optimism.

Figure 2. Life Orientation Test- Revised

Four-item optimism questionaire (4Q)

Below you will find some statements,
You are expected to indicate what best applies to how you felt during the last week including today

	Fully in agreement	Parially in agreement	Not in agreement	Don't know
1. I still expect much from life	(2)	(1)	(0)	(1)
2. I do not look forward to what lies ahead for me in the years to come	(0)	(1)	(2)	(1)
3. My days seem to be passing by slowly	(0)	(1)	(2)	(1)
4. I am still full of plans	(2)	(1)	(0)	(1)

Note
Of the four items that are scored, two are keyed in a positive direction and two in a negative direction. Negatively worded items (i.e. items 2 and 3) are reversely coded before scoring. The additional answer category 'do not know' is coded as the midpoint (coded as 1). The total score ranges from 0 to 8, and higher scores indicate greater optimism.

Figure 3. Four-item optimism questionnaire

Scale for Subjective Well-being of Elderly optimism subscale (SSWO-Optimism)

Below you will find some statements that refer to general well-being. You are expected to indicate what applies best to you. There are no 'true' or 'false' answers. Please try to be as honest and take your time in completing this questionaire.

1. The feeling that life is full of promises I have...	**Very often** (2)	**Sometimes** (1)	**Hardly ever** (0)
2. I still expect much of life.	**Agree** (2)	**Don't know** (1)	**Don't agree** (0)
3. Moments of happiness I have...	**A lot** (2)	**Not very often** (1)	**Almost never** (0)
4. I do not make future plans any more.	**Agree** (0)	**Don't know** (1)	**Don't agree** (2)
5. Happy laughter occurs to me...	**Hardly ever** (0)	**Sometimes** (1)	**Very often** (2)
6. I am still full of plans.	**Agree** (2)	**Don't know** (1)	**Don't agree** (0)
7. I am in good spirits...	**Very often** (2)	**Pretty often** (1)	**Hardly ever** (0)

Note
Of the seven items that are scored, two of the answer categories are keyed in a positive direction and five in a negative direction. Negatively keyed items (i.e. items 1, 2, 3, 6 and 7) are reversely coded before scoring. The total score ranges from 0 to 14, and higher scores indicate greater optimism.

Figure 4. Scale of Subjective Well-being of the Elderly

Chapter 2

Parental longevity correlates with offspring's optimism in two cohorts of community-dwelling older subjects

Age

Nathaly Rius-Ottenheim
Daan Kromhout
Anton JM de Craen
Johanna M Geleijnse
Roos C van der Mast
Frans G Zitman
Rudi G Westendorp
P Eline Slagboom
Erik J Giltay

Abstract

Dispositional optimism and other positive personality traits have been associated with longevity. Using a familial approach we investigated the relationship between parental longevity and offspring's dispositional optimism among community-dwelling older subjects. Parental age of death was assessed using structured questionnaires in two different population-based samples: the Leiden Longevity Study (n=1252, 52.2% female, mean age 66 years, SD 4) and the Alpha Omega Trial (n=769, 22.8% female, mean age 69 years, SD 6). Adult offspring's dispositional optimism was assessed with the Life Orientation Test-Revised (LOT-R). The association between parental age of death and levels of optimism in the offspring was analyzed using linear regression analysis within each sample and a meta-analysis for the overall effect. In both samples, the parental mean age of death was positively associated with optimism scores of the offspring. The association remained significant after adjustment for age, gender, living arrangement, BMI, smoking status, education, and self-rated health of the offspring. The pooled B-coefficient (increase in LOT-R score per 10-year increase in parental mean age of death) was 0.30 (SE=0.08; P <0.001). In conclusion, parental longevity was positively associated with optimism in adult offspring, suggesting a partial linked heritability of longevity and optimism.

Introduction

Human longevity is a complex trait that runs strongly in families and results from a fortunate interaction between genetic and non-genetic factors (Atzmon *et al*., 2004; Bocquet-Appel & Jakobi, 1990; Gudmundsson *et al*., 2000; Herskind *et al*., 1996; Hjelmborg J *et al*., 2006; Perls *et al*., 2000; Vandenbroucke, 1998; Cournil & Kirkwood, 2001; Finch & Kirkwood, 2000; Finch & Kirkwood, 2000). Identifying which heritable factors predict an extended lifespan has been an important aim of recent studies investigating longevity (Christensen *et al*., 2006). Although the most common design used to investigate predictors of longevity is longitudinal, an alternative design has also proven of value in the study of predictors of longevity. This latter methodological approach is based on the hypothesis that familial patterns of longevity are linked to specific endophenotypes of the offspring (Atzmon *et al*., 2004; Westendorp *et al*., 2009). Earlier studies using a familial approach have shown that there is an association between parental longevity and indicators of cognitive functioning and well-being among the offspring (Yashin *et al*., 2010). Thus, a family-based approach allows to explore the association between longevity and measures of mental well-being without using the longitudinal study design of a classic prospective cohort study.

Dispositional optimism, defined as the generalized tendency to positive outcome expectations (Scheier & Carver, 1985), plays an important role not only in mental health status and subjective well-being, but also in physical health (Scheier & Carver, 1985; Scheier *et al*., 1994; Giltay *et al*., 2004; Giltay *et al*., 2006; Tindle *et al*., 2009). Previous results from our group have shown that dispositional optimism was associated with lower all-cause mortality after a follow-up period of 15 years (Giltay *et al*., 2004). Similarly, other prospective cohort studies investigating the relationship between a slightly different construct of optimism (i.e., explanatory-style optimism) and longevity, found that optimism was a strong predictor of survival in college students after 40 years of follow-up (Brummett *et al*., 2006) and older men after 10 years of follow-up (Kubzansky *et al*., 2001). Also neuroticism, a construct inversely correlated to optimism, has been negatively associated with longevity in longitudinal studies (Shipley *et al*., 2007; Terracciano *et al*., 2008; Weiss *et al*., 2009; Wilson *et al*., 2004). However, while these studies were conducted in a given birth cohort, the present study did not use a prospective design as longevity data from one generation were analyzed in relation to the levels of optimism in the next generation (i.e., a cross-generational association study).

The present study was conducted to examine whether parental longevity is associated with dispositional optimism in the offspring. To address this question, we evaluated the intergenerational association between parental longevity and dispositional optimism of the offspring using a family-based approach. We analyzed this association in two independent samples of community-dwelling older subjects and hypothesized that long-lived parents would have a more optimistic offspring than those parents who died at an earlier age.

Methods

Study sample

This study was based on data derived from 2021 older subjects who participated in the Leiden Longevity Study (LLS) and the Alpha Omega Trial (AOT). The study design and population characteristics of these samples have been described in detail elsewhere (Schoenmaker *et al*., 2006; Geleijnse *et al*., 2010). Briefly, in the LLS, subjects with long-lived Caucasian parents, together with their partners, were recruited to study predictors of longevity. Families

were eligible for the study if at least two long-lived, full siblings were alive, where men were considered to be long-lived if they were 89 years or older and women if they were 91 years or older. The offspring of the long-lived subjects included in the LLS, and the offspring's partners and their parents, were also approached to participate in the LLS. This second generation (i.e. the offspring and their partners) comprised the present sample, which included a total of 2515 subjects of the middle-aged generation with a low prevalence of cardiovascular and metabolic disease. Of these 2515 participants of the LLS, 1290 subjects were aged 60 years or older (range 60-84 years) and 1252 had complete data of at least one parental age of death and dispositional optimism. Of these 1252 subjects, 880 were offspring of long-lived parents and 372 were partners of the offspring. In the AOT, 4837 subjects aged 60 to 80 years with a documented history of myocardial infarction within 10 years prior to the start of the trial, thus with a high cardiovascular risk, were enrolled in the study (Geleijnse *et al.*, 2010). Of these subjects, the last recruited 769 participants were asked to complete the Life Orientation Test (LOT-R) to measure optimism (van de Rest *et al.*, 2008). All 769 participants who completed the optimism questionnaire provided complete information on parental age of death. All participants signed an informed consent and the studies were approved by the local medical ethics committees.

Parental vital status and age of death

Parental vital status and parental age of death were assessed through structured questionnaires in both samples. Parental vital status was subsequently categorized in "father alive", "mother alive", "both parents alive", and "both parents dead". When one or both parents were alive during the interview, the mean paternal or maternal age of death was imputed within each sample. In other words, in the LLS, an age of 86 years was imputed for maternal age of death and an age of 77 years was imputed for paternal age of death for the living parents. In the AOT, an age of 77 years was imputed for maternal age of death and an age of 72 years was imputed for paternal age of death for the living parents. Parental age of death was calculated using the mean of the maternal and paternal age of death.

Dispositional optimism

Dispositional optimism of the offspring was assessed using the LOT-R. The LOT-R is a 10-item self-report questionnaire with six items that yield an optimism score and four filler items (Scheier *et al.*, 1994). The scale included three negatively stated items which required reversed coding before scale score computation. Subjects were asked to express the extent of their agreement with each of the items, coding their responses on a 5-point Likert-type scale. The LOT-R score ranges from 0-24 (Cronbach's α LLS= 0.67; Cronbach's α AOT= 0.57). For the computation of the optimism scores, one missing item per subject was allowed, being subsequently imputed with the mean of the remaining five of the LOT-R. Higher scores on the LOT-R optimism scale are indicative of higher optimism levels.

Possible confounders

Sociodemographic and clinical parameters were obtained for the offspring. Living arrangement was defined as a dichotomous variable: living alone, or living with a partner or family. Education was also dichotomized into high (i.e., 11 or more years of education, with at least secondary education completed) and low education. Smoking status was classified as non-smoking, former smoking, and current smoking. Body mass index (BMI) was calculated from the measured weight and height. Self-rated health was classified into feeling healthy,

feeling rather unhealthy or feeling unhealthy. Only 64 participants (3.2%) had one or more missing values on the covariables.

Statistical analysis

Sociodemographic and clinical characteristics were examined using chi-square tests for categorical variables and two-sample t-tests for continuous variables. These data are presented as numbers and percentages for categorical variables, and means ± standard deviations for continuous variables.

Multiple linear regression analyses were used to investigate the association between parental longevity and dispositional optimism of the offspring. We defined dispositional optimism of the offspring as our dependent variable and parental longevity as our independent variable. Unstandardized regression coefficients (B) were given per 10-year increase in parental age of death. Multivariable models were applied to adjust for the effect of potential confounders. Model 1 was adjusted for age and gender of the offspring. Model 2 was additionally adjusted for living arrangement, BMI, smoking, education, and self-rated health of the offspring. In addition, the association between parental age of death and dispositional optimism was assessed using a linear mixed model with a random sibship effect to model correlation of sibling data in the LLS. All p-values are two-tailed and considered statistically significant at the level of $p < 0.05$. Data analyses were performed using SPSS for Windows, version 17.0 (Chicago, IL).

Finally, we performed a meta-analysis of the data from both samples to calculate the pooled mean effect sizes (i.e., standardized mean difference) using Comprehensive Meta-analysis (version 2.2.021; Biostat, Englewood, NJ, USA). For each meta-analysis, the Cochrane's Q statistics were calculated as indicators of the heterogeneity of the included studies. The pooled unstandardized regression coefficients (B) were computed using fixed models, as there was no evidence of heterogeneity.

Results

Sociodemographic and clinical characteristics of both sample populations are summarized in Table 1. The mean age of the subjects from the LLS was 66 years (SD=4) and 69 years (SD=6) for the AOT. Subjects from the AOT were more likely to be men, to be living alone, and to have a lower educational level than subjects from the LLS. Subjects from the AOT were also more likely to be current smokers and had a higher BMI than subjects from the LLS. Subjects from the AOT presented a higher cardiovascular risk profile, due to the higher prevalence of myocardial infarction and stroke. Regarding mental well-being, optimism scores were higher among subjects from the LLS compared to subjects from the AOT. Furthermore (as expected from the inclusion criteria), parents of subjects participating in the LLS were more likely to be alive or to have died at a more advanced age. Subjects who were excluded from the analysis differed from those included in the analysis only on self-rated health, which was rated as poorer by the excluded subjects.

Results from the linear regression analysis showed that parental longevity was associated with levels of dispositional optimism in the offspring (Table 2). This association was somewhat stronger for the AOT sample, which was characterized by a higher cardiovascular risk. Multivariable adjustment for potential confounders yielded similar results. A 10-year increase in the mean age of death of the parents was associated with an increase of 0.23 points in the optimism score of the offspring in the LLS, and with an increase of 0.38 points

Table 1. Baseline characteristics of the 2021 subjects in two samples of older subjects

	LLS	AOT
	N=1252	N=769
Age (yr), mean ± SD	66.1 ± 4.4	69.2 ± 5.7
Age (yr), range	60–84	60–81
Gender: n (%)		
• Male	598 (47.8%)	594 (77.2%)
• Female	654 (52.2%)	175 (22.8%)
Living arrangement: n (%)		
• Living with partner	1073 (86.5%)	634 (82.7%)
• Other arrangement	167 (13.5%)	133 (17.3%)
Education: n (%)		
• Low education	816 (65.4%)	649 (85.3%)
• High education	431 (34.6%)	112 (14.7%)
Smoking status: n (%)		
• Never	479 (38.6%)	119 (15.7%)
• Former	627 (50.6%)	495 (65.3%)
• Current	134 (10.8%)	144 (19.0%)
BMI (kg/m2), mean ± SD	25.6 ± 3.6	27.9 ± 4.05
Poor self-rated health, n (%)	132 (10.6%)	198 (25.9%)
Optimism score†, mean ± SD	15.6 ± 3.3	14.6 ± 3.1
Parents' vital status: n (%)		
• Father alive	112 (9.0 %)	5 (0.7%)
• Mother alive	371 (29.9%)	36 (4.7%)
• Both parents alive	34 (2.7%)	2 (0.3%)
• Both parents dead	723 (58.3%)	715 (94.3%)
Age of death of parents (yr), mean ± SD		
• Father	77.9 ± 13.9	71.9 ± 13.2
• Mother	86.9 ± 10.6	77.6 ± 13.4

LLS: Leiden Longevity Study; AOT: Alpha Omega Trial; BMI: body mass index.
Data are presented as n (%), mean (± SD).
Participants had complete data on the LOT scores and the age of death age of at least one of the parents.
† The LLS and the AOT used the LOT-R to measure optimism.

in the optimism score of the offspring in the AOT. Similar findings were found in the LLS when accounting for potential correlation of sibling data in a multilevel analysis (data not shown). Furthermore, results showed that paternal and maternal age of death made an additional contribution to the optimism levels of the offspring; however, in both samples, the contribution of the age of death of the mother was somewhat stronger than that of the father (Table 2).

The results in Table 2 are graphically presented in Figure 1. This figure shows that an increase of the parental mean age of death is positively associated with dispositional optimism scores of the offspring in both samples, with a somewhat stronger association observed for the AOT sample of post-myocardial infarction patients.

In addition, several sensitivity analyses were conducted to examine the association in a number of situations that may have affected our findings. First, we excluded 35 participants who had lost their parents before their twenties, and subsequently excluded 583 participants with at least one living parent. Results from these analyses showed that, also in these cases,

Table 2. Increase in dispositional optimism scores of offspring per 10 year increase in parental age of death.

	LLS		AOT		Overall*		
	B (SE)	P-value	B (SE)	P-value	B (SE)	P value	Cochrane's Q (P-value)
Mean age of death of both parents (per 10 yr):							
• Model 1	0.267 (0.103)	0.01	0.420 (0.113)	<0.001	0.336 (0.076)	<0.001	1.001 (0.32)
• Model 2	0.233 (0.102)	0.02	0.378 (0.113)	0.001	0.298 (0.076)	<0.001	0.907 (0.34)
Mean age of death of father (per 10 yr):							
• Model 1	0.153 (0.070)	0.03	0.150 (0.084)	0.08	0.152 (0.054)	0.005	0.001 (0.98)
• Model 2	0.126 (0.070)	0.07	0.137 (0.085)	0.11	0.130 (0.054)	0.02	0.010 (0.92)
Mean age of death of mother (per 10 yr):							
• Model 1	0.133 (0.083)	0.11	0.298 (0.084)	<0.001	0.215 (0.059)	<0.001	1.952 (0.16)
• Model 2	0.139 (0.082)	0.09	0.271 (0.083)	0.001	0.204 (0.058)	<0.001	1.280 (0.26)

LLS: Leiden Longevity Study; AOT: Alpha Omega Trial.
Results are given as unstandardized B-coefficients by linear regression analysis (with accompanying P-values) per 10 year increase in parental mean age of death.
Model 1: adjusted for age and gender of the offspring.
Model 2: additionally adjusted for living arrangement, body mass index, smoking, education, and self-rated health of the offspring.
***: meta-analysis of the data from the two samples to yield the pooled B-coefficients using a fixed effects model.**

parental age of death was correlated to dispositional optimism levels of the offspring, indicating that adverse childhood life events were not the driving factor for the association under study. An additional sensitivity analysis in the LLS sample showed that the loss of a parent within the preceding six months also did not affect our findings, thus reducing the possibility that grief reactions accounted for lower scores of optimism in the offspring. Similarly, the gender of the last surviving parent had no effect on our results. Next, when analyzing whether associations differed between sons and daughters, we found that among sons the association was somewhat stronger, although the appropriate interaction term was not significant. Finally, imputation of the actual parental age at the moment of the interview in case

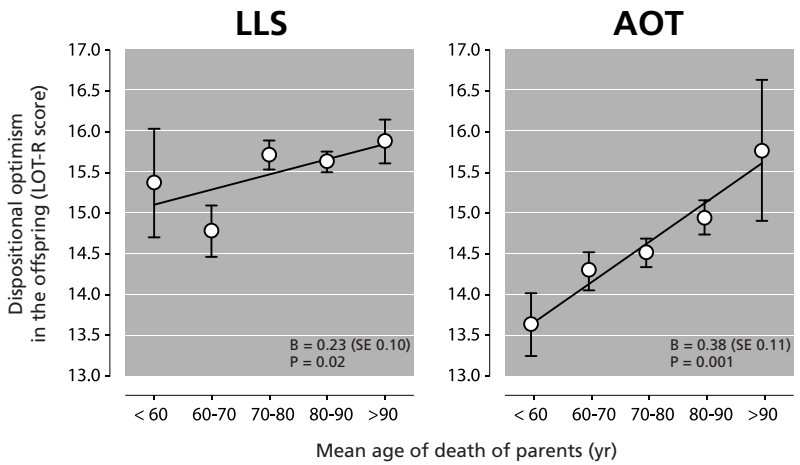

Figure 1. Dispositional optimism of the offspring according to categories of the mean age of death of both parents (i.e., parental longevity). Univariate regression lines are shown with unstandardized B-coefficients analysed by linear regression analysis (per 10 year increase in age of death), adjusted for age, gender, living arrangement, body mass index, smoking, education, and self-rated health of the offspring.

of parents who were still alive in the LLS resulted in persistence of a significant association between parental longevity and offspring's optimism (data not shown).

Results from the meta-analysis showed an overall association between parental longevity and the offspring's optimism scores (Table 2). A 10-year increase in the overall parental mean age of death was associated with an increase of 0.30 SD in the dispositional optimism scores of the offspring.

Discussion

Our results show a positive association between parental longevity and dispositional optimism of the offspring. In other words, our findings indicate that long-lived parents tended to have more optimistic offspring, independently of potential confounders. Longevity of both the father and the mother contributed to the association with dispositional optimism of the offspring. Thus, our results suggest that longevity and dispositional optimism may be intergenerationally associated, based on a design that has been used previously (Martin *et al.*, 2007; Perls & Terry, 2003; Yashin *et al.*, 2010)

An important strength of our study was the consistency of our results in two independent samples of community-dwelling old subjects. Furthermore, this analysis in two different samples allowed us to compare the association between longevity and offspring's endophenotypes in a sample with exceptional long-lived family members with a low cardiovascular risk (LLS) to that found in another sample of post-myocardial infarction patients with families with average lifespans (AOT).

However, some limitations of the study need to be considered. First, the causal direction of the association remains unclear. Second, the findings might reflect ethnicity-specific effects and should therefore be confirmed in other non-Caucasian populations. Third, it should be noted that about a quarter of the LLS subjects were sibling pairs, and therefore not independent, as they shared the same mean age of death of their parents. However, our findings did not change substantially when we accounted for sibling correlation in a linear mixed model analysis. Fourth, because participants in the LLS were selected for longevity of the participants and their sibs, the variability under study in the variables optimism and longevity of the parents might be reduced. This potentially reduced variability may explain the somewhat weaker associations in the LLS as compared to the AOT. Finally, recall bias may have arisen as the level of offspring's optimism may have overestimated the actual age of death of the parents.

To our knowledge, our study is the first to consider the association between parental longevity and offspring's dispositional optimism. Findings from the present study are consistent with the previously described cross-sectional study (Yashin *et al.*, 2010), which also used a familial approach and showed that parental longevity was associated with certain endophenotypic characteristics of the offspring, such as cognition. Using a similar study design, we extend these findings by showing that parental longevity is also associated with personality traits of the offspring. Our findings are also in accordance with a study among 246 centenarians that found that the offspring had lower levels of neuroticism and higher extraversion compared to norm scores (Givens *et al.*, 2009). The present findings also extend previous results of our group and others which showed, in the same generation, a positive association between dispositional optimism and lower (cardiovascular) mortality rates (Giltay *et al.*, 2004; Giltay *et al.*, 2006; Tindle *et al.*, 2009; Chida & Steptoe, 2008).

Although our results show an association between longevity and optimism in two dif-

ferent samples, the underlying mechanisms for this association remain to be elucidated. The association between parental longevity and offspring's optimism may be explained by genetic factors, environmental factors, or a combination of both. Previous family studies have indicated that the two phenotypes longevity and dispositional optimism have a heritable component and may be part of a phenotypical spectrum that is inherited together (Martin *et al*., 2007; Plomin *et al*., 1992). However, shared heritability is only one of the multiple potential mechanisms and the environmental effects should not be underestimated. An increasing body of evidence shows that certain factors in childhood environment, particularly the presence of resources such as parental warmth and financial security, may act as a determinant of both parental longevity and offspring's optimism (Heinonen *et al*., 2005; Heinonen *et al*., 2006). For instance, offspring may resemble their parents in their health-promoting behaviors, such as smoking habits, alcohol use, dietary patterns, and physical activity (Repetti *et al*., 2002; Zhang *et al*., 2004), arising through the effects of reflection and learning. Moreover, this mirroring effect may also influence the offspring's coping styles and stress reactivity to adverse life events. Alternatively, offspring's optimism may affect longevity of the parents through increased social support and maintenance of the parental role. In this way, offspring's support may buffer parental distress by mediating environmental stresses that threaten to overwhelm the coping abilities of the older parent (Silverstein & Bengtson, 1991; Okamoto & Tanaka, 2004; Zunzunegui *et al*., 2009).

In our study, optimism levels of the offspring were the highest when both parents were long-lived. However, maternal longevity was slightly more strongly associated with offspring's optimism than paternal longevity. These findings are consistent with the results of some studies that investigated the relative importance of the sex-specific transmission of heritable factors on longevity (Yashin *et al*., 2010; Brand *et al*., 1992). The authors suggested that the stronger effect of maternal longevity on offspring's characteristics might be primarily mediated through shared heritable factors, either genetic or non-genetic (Brand *et al*., 1992). Nevertheless, environmental factors are also likely to play an important role in the differential inheritance of longevity. Either way, potential recall biases should also be taken into account when evaluating sex-specific differences in longevity, as it is possible that interviewed participants may better recall their mother's than their father's lifespan.

In conclusion, our findings suggest that parental longevity, particularly maternal longevity, is associated with offspring's dispositional optimism. These results may help to understand the mechanisms of familiar transmission of human longevity and the role of optimism. However, further studies are warranted to disentangle the potential causal relationships between lifespan and dispositional optimism.

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Chapter 3

Telomere length and mental well-being in elderly men from the Netherlands and Greece

Behavior Genetics

Nathaly Rius-Ottenheim
Joyce M Houben
Daan Kromhout
Anthony Kafatos
Roos C van der Mast
Frans G Zitman
Johanna M Geleijnse
Geja J Hageman
Erik J Giltay

Abstract

Telomeres, repetitive DNA sequences that promote chromosomal stability, have been related to different measures of mental well-being and self-rated health, but mainly in women during adulthood. We aimed to investigate whether accelerated telomere shortening is associated with poor mental well-being and poor self-rated health in community-dwelling elderly men. Leukocyte telomere length was measured using quantitative PCR in two different samples of 203 elderly men (mean age 78 years) from the Netherlands in 1993, and 123 elderly men (mean age 84 years) from Greece in 2000. We also obtained follow-up data in 2000 from 144 Dutch subjects, of whom 75 had paired telomere length data in 1993 and 2000. Mental well-being was conceptualized as dispositional optimism, depressive symptoms, cognitive functioning, and loneliness. Linear regression analyses were used to study the association between telomere length, measures of mental-well being, and self-rated health, while adjusting for potential confounders. In cross-sectional analyses, leukocyte telomere length was not associated with measures of mental well-being and self-rated health, neither in the Netherlands nor in Greece. Also, the rate of leukocyte telomere shortening (mean decrease: 0.28 kbp over 7 years) in the 75 Dutch participants with longitudinal data was not associated with changes in different measures of mental well-being and self-rated health. Thus, our results provide no support for a relationship between leukocyte telomere length and mental well-being in elderly community-dwelling men.

Introduction

Telomeres are repetitive DNA sequences that cap chromosomal ends and play a critical role in promoting chromosomal stability (Blackburn, 2001). Telomeres shorten with every cell division and, after reaching a critical length, eventually induce cellular senescence and apoptosis (Allsopp *et al*., 1992). Therefore, the capacity of cellular replication is modulated by processes that either accelerate or counter telomere shortening; for instance through the elongating effect of the enzyme telomerase (Greider, 1996). Cellular environment also plays an important role in regulating telomere length. It has been shown that exposure to physical stressors –most convincingly shown for oxidative stress by reactive oxygen species– can hasten telomere shortening and lead to premature cell senescence (Gilley *et al*., 2008; Richter & Von Zglinicki, 2007). Thus, telomere length reflects the cellular replicative history and the presence of many stressors at the cellular level. Besides replication timing, telomeres also participate in nuclear processes such as chromosome positioning in the nucleus, transcriptional repression, and heterochromatin formation (Taddei & Gasser, 2004)Therefore, telomeres have been considered markers of biological aging, age-related diseases, and mortality (Benetos *et al*., 2001; Cawthon *et al*., 2003; Epel *et al*., 2009).

Several components of mental well-being decline with aging (Reiche *et al*., 2004) and are associated with an excessive activation of different stress systems. It has been hypothesized that oxidative stress through free radicals may be involved in accelerated telomere shortening in case of poor mental health states (Hovatta *et al*., 2010), although the detailed molecular mechanisms involved are still poorly understood. Environmental factors involved are stress, diet, smoking, substance abuse, and physical exercise (Nordfjall *et al*., 2008; Valdes *et al*., 2005). There is a rapidly growing literature on the link between poor mental well-being and telomere shortening. Several cross-sectional studies that included middle-aged (mean age ranging from 27 to 65) subjects documented a shorter mean telomere length in relation to different measures of poor mental well-being such as in case of unipolar and bipolar mood disorders (Damjanovic *et al*., 2007; Simon *et al*., 2006), dispositional pessimism (O'Donovan *et al*., 2009), cognitive impairment and decline (Valdes *et al*., 2010; Yaffe *et al*., 2009), Alzheimer's disease (Honig *et al*., 2006; Panossian *et al*., 2003), and childhood trauma (Kananen *et al*., 2010; Tyrka *et al*., 2009). In addition, increased psychological stress and poor self-rated mental health were also been related to shorter telomeres (Epel *et al*., 2004; Parks *et al*., 2009). Studies among elderly subjects, however, did not find a clear association between telomere length with depressive symptoms or personality traits (i.e. type D personality) among 890 older patients with chronic heart failure (Huzen *et al*., 2010). We are not aware of studies that prospectively studied changes in telomere length over time in relation to changes in measures of mental well-being, as prior studies had a case–control design, a cross-sectional design, or did not measure telomere length sequentially.

Although there is evidence of a relationship between telomere shortening and poor mental well-being during adulthood, it is unclear whether such an association persists in late life. We tested the hypothesis that shorter telomeres would be associated with poor well-being in data collected in the Netherlands and Greece.

Methods

Study sample

For the present study we used data from the Zutphen Elderly Study (the Netherlands) and the Cretan Elderly Study (Greece). The Zutphen Elderly Study consisted of 553 men in 1993, of whom 390 were willing to participate (response rate 71%), and 345 had a blood sample. However, only 203 buffy coats could be used for DNA isolation since 142 samples were not available for testing. These data were missing at random, and participants with unavailable DNA did not differ in any baseline characteristics from the participants included in the analyses. For the follow-up examination in 2000, 176 men enrolled in the study in Zutphen. Blood samples were available from 146 individuals. Because of the insufficient quality of the DNA of two of the participants, 144 men (82%) were finally included in the present analysis. Of these 144 Dutch men who were included in the analysis in 2000, 75 men had also a blood sample available in 1993. We only had data of the Cretan sample in 2000, and not in 1993. The Cretan sample consisted of 165 men in 2000. Of these men, 152 were willing to participate (response rate 92%) and blood samples were drawn from 129 individuals. In six men, the concentration of DNA was not sufficient to determine telomere length, yielding information on 123 Cretan men for subsequent analysis. The study was approved by local medical ethics committees.

Leukocyte telomere length measurement

Non-fasting blood samples were collected in the morning into citrate tubes. Buffy coats were obtained for subsequent DNA isolation. Samples from Zutphen were stored at –30 °C before transport within a few days of collection to the National Institute for Public Health and Environment (RIVM), the Netherlands. Samples from Crete were firstly stored at –80°C and subsequently transported to the Netherlands on dry ice by plane. After arriving at the RIVM, all samples were stored at –80°C. The change in temperature storage did not affect the DNA quality, since DNA is stable at a temperature below –20 °C (Kohler *et al.*, 1997). The DNA used for measurement of telomere length was extracted from a 200 µl buffy coat sample by a single person, within a 4-week period, using QIAamp DNA Mini Kit (Qiagen, Venlo, the Netherlands) according to the manufacturer's protocol. The DNA was quantified using a Nanodrop instrument (Isogen Life Science, Belgium). The samples from Crete and Zutphen were processed simultaneously.

Leukocyte telomere length was determined by quantitative polymerase chain reaction (qPCR) as described by Cawthon (Cawthon, 2002). The qPCR assay for the telomere length measurement was done within a 4-week period following the extraction of DNA. Two master mixes were prepared, one with telomere primers and one with Human β globin (HBG) primers (1x IQ SYBRgreen supermix from BioRad, CA, USA). To confirm reproducibility of the applied method, we repeated for 20 samples the leukocyte telomere length measurement by using an additional reference gene, acidic ribosomal phosphoprotein PO (36B4), 300 nM forward primer (5'-CAGCAAGTGGGAAGGTGTAATCC -3'), 500nM reverse primer (5'- CCCATTCTATCATCAACGGGTACAA -3'). The estimated R-square for the measurement with the extra reference gene was 0.76 ($p<0.001$). This confirmed the reproducibility of the leukocyte telomere length measurement, with a coefficient of variation for the triplicates of the telomere reaction being 4.1% and for the reference gene was 3.0%. Sample DNA was pippeted into a 96-wells plate at a final concentration of 10 ng/µl. Subsequently, 20µl of the mastermix was added and the plate was briefly centrifuged. Each sample was run

in triplicates. The triplicates were located on the same qPCR-plate and for the reference gene the triplicates were located on another qPCR-plate but in the same positions. For the standard curve a reference DNA sample was diluted serially to produce three concentrations of 1.25, 5, and 10 ng/µl. In every run, negative controls (MQ + mastermix) and reference samples were included. The references were derived from two different Hela cell lines, one with relatively short telomeres (Hela S3: 5.5 kb) and one with long telomeres (Hela 229: 14-15 kb). By adding reference DNA of controls to each qPCR, a standard curve could be created and the absolute telomere length of the samples could be calculated as kilo-base pairs (kbp). The matched 75 samples of the Zuthpen Elderly Study were run in the same plate. Hela cell lines were kindly provided by Prof. Alexander Bürkle, University of Konstanz, Germany. The quantitative polymerase chain reaction (qPCR) was performed using a BioRad MyiQ iCycler Single Color RT-PCR detection system using iQTM SYBR® Green Supermix, containing iTaq Polymerase, dNTPs, SYBRGreen I, and buffers (BioRad, CA, USA).

Measures of mental well-being

Depressive symptoms were assessed in both samples in 2000 using the 15-item version of the Geriatric Depression Scale (GDS-15). The GDS-15 is a validated instrument to screen for depressive symptomatology in older people as it excludes somatic symptoms that might also be related to physical illnesses (Yesavage *et al.*, 1982). The GDS-15 score ranges from 0 to 15 points. Depressive symptoms were additionally assessed in 1993 and 2000, only in Zutphen (The Netherlands), using the Dutch translation of the Zung self-rating depression scale (Zung SDS). The index score of the Zung SDS (i.e., [sumscore/80] x 100) varies from 25 to 100 points (Kitchell *et al.*, 1982; Okimoto *et al.*, 1982; Zung, 1965).

Dispositional optimism was assessed in all participants of both samples in 1993 and 2000 using a four-item questionnaire (Giltay *et al.*, 2006) consisting of the following statements – "I still expect much from life", "I do not look forward to what lies ahead for me in the years to come", "My days seem to be passing by slowly", and "I am still full of plans" (our translations). Within the four score items, two negatively stated items required reversed coding. The additional answer category "do not know" was also coded as the midpoint (score 1). The optimism questionnaire score ranges from 0-8 points, higher scores being indicative of higher optimism levels. For the computation of the optimism score only one missing item per subject was allowed, being subsequently imputed with the mean of the remaining three items. Internal consistency was of moderate strength (Cronbach's alpha was 0.63 in 2000).

Global cognitive function was tested in 1993 and 2000 only in the Zutphen sample (The Netherlands). The assessment was performed by a trained nurse or interviewer using the 30-point Mini-Mental State Examination test (MMSE) (Folstein *et al.*, 1975). This occurred in a protocolized way in which care was taken to prevent other persons (e.g. wife) to assist the participant during the MMSE testing.

Feelings of loneliness were assessed in both samples in 1993 and 2000 using the Loneliness Scale of De Jong Gierveld. The loneliness scale comprises 11 items, with responses coding on a 0-5 Likert scale. A sample questionnaire item is "I find my circle of acquaintances too limited". The loneliness score ranges from 0 to 11 points (Scharf & De Jong-Gierveld, 2008). This scale has been shown to have good internal consistency (Cronbach's alpha 0.82) (De Jong-Gierveld & Kamphuis, 1985).

Participants were asked to report their health status through a single-item question: "How would you describe your current health status". There were five possible answers to this question, ranging from excellent to bad health.

All questionnaires were translated to the participant's native language (Dutch or Greek).

Possible confounders

Sociodemographic, lifestyle, and morbidity parameters were obtained using protocolized structured questionnaires (Keys *et al.*, 1966). Living arrangement was dichotomized as living alone or with others; smoking status as smokers and non smokers; and alcohol consumption as users and non-users. Body mass index (BMI) was calculated by dividing body weight (kg) by the squared height (m) of the participant. Physical activity was assessed with a validated questionnaire designed for retired men to calculate the total minutes per week spent in different physical activities (i.e. walking, cycling, gardening, odd jobs, sports, hobbies, and work) (Caspersen *et al.*, 1991). Presence of chronic diseases, defined as having either cardiovascular diseases (i.e. stroke, myocardial infarction, or heart failure), diabetes mellitus or cancer, was determined by a survey questionnaire and confirmed with hospital discharge data and written information from the general practitioner.

Statistical analysis

Baseline and follow-up telomere length were normally distributed. As MMSE scores were negatively skewed (due to the ceiling effect of the maximum score of 30), 32 minus the score was log-transformed and inverted to normalize the distribution. Physical activity was positively skewed and logarithmically transformed before the analyses. Geometric means are presented with 10th and 90th percentiles [P10; P90]. Other data are presented as numbers and percentages for categorical variables, and means ± standard deviations, or medians with interquartile ranges for continuous variables (when appropriate). The decline in telomere length over time in the Zutphen sample was tested by t-test for paired samples.

Linear regression was used to analyze the cross-sectional and longitudinal associations of leukocyte telomere length with self-rated health, and measures of mental well-being (i.e. dispositional optimism, depressive symptoms, cognitive function, and loneliness). Multivariate models were applied to adjust for the effect of potential confounders. Firstly, we tested the association between leukocyte telomere length and mental well-being or self-rated health in a crude model. Subsequently, we adjusted for age. Finally, we additionally adjusted for the following covariates: living arrangement, smoking status, alcohol consumption, physical activity, chronic diseases, and BMI. Sensitivity analyses were conducted after excluding subjects with a history of cardiovascular disease, diabetes mellitus, or cancer.

An additional linear regression analysis was used to assess associations between changes in leukocyte telomere length and changes in measures of poor mental well-being and self-rated health. Again, multivariate models as described above were applied to adjust for the effect of potential baseline confounders.

All p-values are two-tailed and considered statistically significant at the level of $p<0.05$. Data analyses were performed using SPSS for Windows, version 17.0 (Chicago, IL).

Results

Sociodemographic and clinical characteristics of both samples are summarized in Table 1. The mean age of men from Zutphen in 1993 was 78 years (range 72–91); whereas in 2000, the mean age of men from both Crete and Zutphen was 84 years old (range 79–98). In 2000, Cretan elderly men had longer telomeres (mean telomere length 5.0 kbp) than elderly men from Zutphen (mean telomere length 4.8 kbp; $p<0.001$). Regarding mental well-being, Cretan elderly men were less optimistic and showed more depressive symptoms than elderly

men from Zutphen (p<0.001). Although more Cretan elderly men rated their health status as poor, they were less likely to have chronic diseases compared to elderly men from Zutphen (p<0.001). Finally, Cretan elderly men reported more physical activity than elderly men from Zutphen (p<0.001).

Table 1. Baseline characteristics of elderly men from the Netherlands (Zutphen) in 1993 and 2000 and Crete (Greece) in 2000

Variables	Zutphen		Crete
	1993	2000	2000
Number of participants	203	144	123
Age (years), mean (range)	77.6 (72.0-91.0)	84.1 (79.5-98.2)	84.1 (79.2-93.4)
Telomere lenght mean ± SD	5.0 ± 0.5	4.8 ± 0.3	5.0 ± 0.5
GDS score, median (IQR)	-	2 (1-4)	3 (1-7)
Zung score, median (IQR)	42.5 (26.3-66.3)	46.3 (38.8-50.0)	-
Dispositional optimism, median (IQR)	6 (4-7)	5 (4-6)	4 (2-6)
MMSE, median (IQR)	27 (25-28)	28 (26-29)	-
Loneliness, median (IQR)	1 (0-3)	2 (0-5)	3 (1-5)
Living alone, (%)	45 (22.3%)	56 (38.9%)	23 (19.8%)
Current smoking, (%)	55 (29.1%)	14 (9.7%)	11 (8.9%)
Alcohol users, (%)	141 (76.2%)	110 (76.4%)	66 (55.5%)
Body Mass Index, mean ± SD	25.6 ± 2.6	25.6 ± 3.7	24.9 ± 4.2
Physical activity, (min/week), median (P10, P90)	513 (125; 1369)	210 (0; 835)	397 (0; 1440)
Chronic diseases, n(%)	59 (29.1%)	70 (48.6%)	29 (23.6%)
Self-rated health, n(%)			
• Excellent	22 (10.9%)	7 (4.9%)	9 (7.6%)
• Very good	93 (46.0%)	19 (13.3%)	13 (11.0%)
• Good	74 (36.6%)	86 (60.1%)	34 (28.8%)
• Poor	10 (5.0%)	29 (20.3%)	39 (33.1%)
• Bad	3 (1.5%)	2 (1.4%)	23 (19.5%)

Data are presented as n(%), mean (±SD), or median (IQR) when apppropriate.

† Cronic disease was defined as having prevalent cardiovascular disease (i.e. myocardial infarction, stroke, heart failure) cancer, or diabetes mellitus.

Table 2. Association of telomere lenght with measures of mental well-being and self-rated health in older men from Zutphen and Crete

Variables	Zutphen								Crete			
	1993				2000				2000			
	No.	Beta	Test	P-value	No.	Beta	Test	P-value	No.	Beta	Test	P-value
Depressive symptoms (Zung SDS)												
• Crude association	171	-0.004	t(168)=-0.05	0.96	136	-0.039	t(133)=-0.46	0.65			-	
• Model 1*	171	0.006	t(167)= 0.07	0.94	136	-0.020	t(132)=-0.23	0.82			-	
• Model 2¶	167	0.023	t(155)= 0.28	0.78	135	-0.077	t(123)=-0.90	0.37			-	
Depressive symptoms (GDS_15)												
• Crude association			-		122	-0.099	t(119)=-1.09	0.28	102	-0.121	t(99)=-1.22	0.22
• Model 1*			-		122	-0.051	t(118)=-0.54	0.59	102	-0.044	t(98)=-0.44	0.66
• Model 2¶			-		122	-0.071	t(112)=-0.77	0.44	88	-0.000	t(78)=-0.003	0.99
Optimism score (4-item questionnaire)												
• Crude association	201	-0.025	t(198)=-0.35	0.73	142	-0.074	t(139)=-0.87	0.38	117	0.049	t(114)= 0.53	0.60
• Model 1*	187	-0.041	t(183)=-0.57	0.57	142	-0.148	t(138)=-1.82	0.07	117	0.026	t(113)= 0.28	0.78
• Model 2¶	178	-0.018	t(168)=-0.24	0.81	141	-0.128	t(131)=-1.53	0.13	101	0.014	t(91)= 0.15	0.88
Cognitive function (MMSE)												
• Crude association	183	0.010	t(180)= 0.14	0.89	137	-0.119	t(134)=-1.39	0.17			-	
• Model 1*	183	-0.021	t(179)=-0.30	0.77	137	-0.144	t(133)=-1.66	0.10			-	
• Model 2¶	173	0.003	t(163)= 0.03	0.97	136	-0.099	t(126)=-1.06	0.29			-	
Loneliness (de Jong Gierveld)												
• Crude association	189	0.032	t(186)= 0.44	0.66	140	-0.036	t(137)=-0.43	0.67	115	-0.001	t(112)=-0.01	0.99
• Model 1*	179	0.088	t(175)= 1.17	0.24	140	-0.038	t(136)=-1.44	0.66	115	0.006	t(111)= 0.06	0.95
• Model 2¶	170	0.109	t(160)= 1.43	0.16	139	-0.040	t(129)=-1.45	0.65	99	-0.032	t(89)=-0.31	0.76
Selfrated health												
• Crude association	202	-0.002	t(199)=-0.03	0.98	143	-0.071	t(140)=-0.84	0.40	118	0.036	t(115)= 0.38	0.70
• Model 1*	188	0.024	t(184)= 0.33	0.74	143	-0.066	t(139)=-0.77	0.44	118	0.067	t(114)= 0.75	0.46
• Model 2¶	178	0.035	t(168)= 0.46	0.64	142	-0.089	t(132)=-1.04	0.30	102	0.110	t(92)= 1.30	0.20

Results are obtained with linear regression analysis and presented as betas with P-values

* Adjusted for age.

¶ Additionally ajusted for living arrangement, alcohol consumption, physical activity, chronic diseases, smoking status, and BMI.

Table 3. Associations between changes in mental well-being and sefrated health and changes in telomere length in 75 older men from Zutphen from 1993 till 2000

Variables	Δ Telomere length		
	Beta	Test	P-value
Δ Depressive symptoms (Zung SDS)			
Crude association	-0.061	t(57)=-0.47	0.64
Model 1*	-0.058	t(56)=-0.45	0.66
Model 2¶	-0.006	t(48)=-0.05	0.96
Δ Optimism score (4-item questionnaire)			
• Crude association	-0.013	t(71)=-0.11	0.92
• Model 1*	-0.008	t(68)=-0.07	0.95
• Model 2¶	0.017	t(59)= 0.14	0.89
Δ Cognitive function (MMSE)			
• Crude association	0.084	t(64)= 0.68	0.50
• Model 1*	0.092	t(63)= 0.75	0.46
• Model 2¶	0.074	t(54)= 0.55	0.58
Δ Loneliness (de Jong Gierveld)			
• Crude association	0.060	t(66)= 0.49	0.62
• Model 1*	0.070	t(63)= 0.56	0.58
• Model 2¶	0.106	t(54)= 0.80	0.43
Δ Selfrated health			
• Crude association	0.022	t(70)= 0.18	0.86
• Model 1*	0.033	t(67)= 0.27	0.79
• Model 2¶	0.122	t(58)= 0.96	0.34

Results are obtained with linear regression analysis and presented as betas with P-values

* Adjusted for age.

¶ Additionally ajusted for living arrangement, smoking status, alcohol consumption, physical activity, chronic diseases, and BMI.

Table 2 shows the results from the linear regression analyses for the elderly men from Zutphen and Crete. We found no statistically significant associations between leukocyte telomere length with self-rated health or any measure of mental well-being. In an additional analysis in men from Zutphen in 1993, we found no differences in telomere length among groups categorized according to quartiles of the MMSE (mean TL of 4.99 vs. 5.08 in lower versus upper quartile with MMSE≤23 and ≥29 points; p=0.42). Sensitivity analyses in elderly men free from chronic diseases confirmed the absence of any tendency towards an association between leukocyte telomere length and self-rated health or mental well-being (data not shown). Multivariate adjustments for potential confounding factors did not alter these results (i.e., Models 1 and 2).

Additional analysis of the paired DNA samples from 75 Dutch participants with data in 1993 and in 2000 showed that the mean telomere length in 1993 was 5.03 kbp, whereas the mean telomere length in 2000 was 4.76 kbp. The mean decline in leukocyte telomere length during 7 years of follow-up was 40.2 bp per year (95% confidence interval [CI]: 26.9-53.5; p<0.001), as previously described (Houben *et al.*, 2011). Although most individuals showed a decrease in telomere length, for 12 participants (16%) we found an increase. Pearson's correlation coefficient showed a moderately strong relationship between telomere length in 1993 and 2000 in 75 men (r=0.51; p<0.001). Results from the linear regression analysis showed no association between absolute changes in leukocyte telomere length and absolute changes in any measure of mental well-being or self-rated health over seven years of follow-up (Table 3). When we used relative changes of telomere length (TL in 2000 minus TL in 1993 divided by TL in 1993) instead of absolute changes (TL in 2000 minus TL in 1993) similar results were found.

Discussion

The current study examined the association between telomere length, mental well-being, and self-rated health in two samples of elderly men (over 70 years old) from two different European countries. In contrast to previous studies among younger adults (Simon *et al.*, 2006; O'Donovan *et al.*, 2009; Panossian *et al.*, 2003; Honig *et al.*, 2006; Tyrka *et al.*, 2009; Epel *et al.*, 2004), our results revealed no cross-sectional associations between leukocyte telomere length and measures of mental well-being or self-rated health, neither in the Netherlands nor in Greece. Furthermore, the longitudinal analysis of data from 75 men with measurements in 1993 and 2000 showed neither an association between the telomere shortening rate and changes in mental well-being or self-rated health.

Among the strengths of the present study is the analysis of a wide range of mental well-being variables in relation to telomere length. The longitudinal study design allowed us to identify the determinants of leukocyte telomere length change in a relatively large cohort of community-dwelling elderly subjects. Furthermore, we used the validated qPCR technique including shorter and longer sized standard samples to assess telomere length instead of the more time-consuming Southern Blot (Cawthon, 2002). Also noteworthy is the international design of this study. Our results were consistent in two different population-based samples of different origin and advanced age. Although we did not find statistically significant associations between telomere length and mental wellbeing, our findings suggest that the rate of telomere shortening varied across countries. The observed longer telomeres in Cretan men compared to men from Zutphen may partly be explained by different lifestyles. It is well-known that inhabitants from Mediterranean countries usually engage in healthier lifestyles than people from Northern European countries (Trichopoulou & Lagiou, 1997). In our study, participants from Crete spent more time in physical activities than participants from Zutphen. Furthermore, it is possible that the Mediterranean diet (more habitual in Crete) incorporates more antioxidants that may buffer telomere shortening through reduction of oxidative stress (Dai *et al.*, 2008; Buijsse *et al.*, 2007). However, several limitations should be considered in the interpretation of our results. First, the elderly men had all survived until old age, meaning that they were aging relatively well. Given that cell aging processes are considered to be related to life expectancy, it is possible that the advanced age of our sample hampered the detection of a relationship between telomere length and markers of mental well-being. A second explanation may be that our study was only composed of men, which limits the generalization of our results to women, while many of the previous studies with positive findings included only women (O'Donovan *et al.*, 2009; Valdes *et al.*, 2010; Epel *et al.*, 2004; Parks *et al.*, 2009), a majority of women (Tyrka *et al.*, 2009; Kananen *et al.*, 2010; Damjanovic *et al.*, 2007), or about 50% women (Simon *et al.*, 2006; Yaffe *et al.*, 2009). Third, associations may exist in clinical samples with neuropsychiatric diseases rather than epidemiological samples from the general population. Fourth, methodological error likely played a minor role, because the measurement method was rigorously tested and calibrated, and both telomere length measurements were in line with previously reported mean telomere length in this age range (Slagboom *et al.*, 1994). Yet, a limitation of our study was that telomere length was assessed in stored buffy coats, whereas it should preferably be measured in peripheral blood mononuclear cells (PBMCs) obtained from fresh buffy coats (Choi *et al.*, 2008). Moreover, the 4-item optimism questionnaire has not been validated yet and we relied on self-report measures rather than semi-structured psychiatric interviews for mental-wellbeing measures (except for the MMSE). Another limitation would be that we did

not measure telomerase activity. Finally, though our sample was relatively large compared to most of the earlier studies among older subjects, it is possible that type II error has arisen and hampered the detection of positive associations. Therefore, future studies in larger samples are needed to confirm our results.

Although our findings contrast with several previously reports, our findings are in line with a study among 890 patients with chronic heart failure (61% male, with a mean age of 73 years), which found no association between telomere length and self-reported depressive symptoms or the type D personality trait (Huzen *et al.*, 2010). Although a relationship seems to exist during adulthood, leukocyte telomere length may no longer be related to mental well-being in the oldest old subjects. There is also evidence that there is less telomere length variation in the healthy elderly subjects versus younger subjects (Halaschek-Wiener *et al.*, 2008). Moreover, there may be a higher degree of telomere length instability in older subjects, which may also explain our null findings (Harris *et al.*, 2006; Martin-Ruiz *et al.*, 2005). The instability of telomere length in the old age is thought to derive from an altered function of the enzyme telomerase, but this hypothesis is yet to be confirmed. In the current Dutch cohort, we previously found that telomere length did not predict mortality at old age (Houben *et al.*, 2011), similar to the subgroup of participants aged 75 years or older, in which telomere length was also no longer a significant predictor of mortality (Cawthon *et al.*, 2003).

Mental well-being is known to deteriorate in old age. Dispositional optimism declines with age (Giltay *et al.*, 2006), whereas self-reported depressive symptoms (Barefoot *et al.*, 2001; Davey *et al.*, 2004), cognitive function (Schonknecht *et al.*, 2005), and loneliness (Cohen-Mansfield *et al.*, 2009) increase over time. It has been suggested that psychosocial or biological stressors might act as mediators between telomere shortening and measures of poor mental well-being or self-rated health, for instance through increased oxidative stress on cellular level (Hovatta *et al.*, 2010; Tyrka *et al.*, 2009). Although some studies did find evidence of an association between higher levels of oxidative stress and measures of poor mental well-being including dementia and depression (Simon *et al.*, 2006; Damjanovic *et al.*, 2007; Valdes *et al.*, 2010; Yaffe *et al.*, 2009; Panossian *et al.*, 2003), the mechanism underlying the transduction of such stressors to oxidative stress on cellular level remains to be further elucidated.

In summary, our results provide no support for the relationship between leukocyte telomere length and mental well-being or self-rated health in elderly men.

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Chapter 4

C-reactive protein haplotypes and dispositional optimism in obese and non-obese subjects

Inflammation Research

Nathaly Rius-Ottenheim
Anton JM de Craen
Johanna M Geleijnse
P Eline Slagboom
Daan Kromhout
Roos C van der Mast
Frans G Zitman
Rudi G Westendorp
Erik J Giltay

Abstract

Background Chronic low-grade inflammation, characterized by elevated plasma levels of C-reactive protein (CRP), has been inversely associated with dispositional optimism. Using a Mendelian randomization design, this study explored whether CRP haplotypes that determine CRP plasma levels are also associated with dispositional optimism.
Methods In a sample of 1084 community-dwelling subjects (aged 60-85 years) from three cohort studies (Arnhem Elderly Study, n=426; Leiden Longevity Study, n=355; Zutphen Elderly Study, n=303), six CRP polymorphisms (rs2808628, rs2808630, rs1205, rs1800947, rs1417938, and rs3091244) coding for five common haplotypes were genotyped. The association of CRP haplotypes with CRP plasma levels and dispositional optimism was analyzed using multivariable linear regression models. Subanalyses were stratified for body mass index (BMI≥ 25 kg/m2).
Results CRP haplotypes determined CRP plasma levels (adjusted beta= 0.094, p<0.001). In the whole group, no association was found between CRP haplotypes and dispositional optimism scores (adjusted beta= −0.02, p=0.45). In BMI strata, CRP haplotypes were associated with increasing levels of plasma CRP levels (adjusted beta=0.112; p=0.002) and lower dispositional optimism levels (adjusted beta= −0.068; p=0.03) in the obese group only.
Conclusions These results suggest that genetically increased CRP levels are involved in low dispositional optimism, but only in case of obesity.

Introduction

Chronic low-grade inflammation is proposed as one of the underlying mechanisms through which psychological factors influence a range of health outcomes (Ranjit *et al*., 2007), including mortality risk (Steptoe *et al*., 2007; Carney *et al*., 2002). Although most studies addressing the association between inflammation and mood states have focussed on the link with negative affect (Bremmer *et al*., 2008; Danner *et al*., 2003; Ford & Erlinger, 2004; Kop *et al*., 2002; Penninx *et al*., 2003), there is increasing evidence for an association between inflammation and positive affect (Friedman *et al*., 2007; Janicki-Deverts *et al*., 2007; Roy *et al*., 2010; Steptoe *et al*., 2005). These studies reported an inverse association of positive affective states with pro-inflammatory acute-phase proteins and cytokines, such as interleukin-6 (IL-6) (Janicki-Deverts *et al*., 2007; Friedman *et al*., 2007) and plasma fibrinogen (Steptoe *et al*., 2005; Roy *et al*., 2010).

Inflammation is also associated with the positive affective trait dispositional optimism, which is defined as the generalized expectancy of positive outcomes for the future (Scheier *et al*., 1994). Dispositional optimism has been associated with better outcomes in mental and physical health (Carver *et al*., 2010; Giltay *et al*., 2004a; Giltay *et al*., 2006; Tindle *et al*., 2009). These benefits may result from the more effective coping used by optimists and its effects on stress resilience. It is suggested that a greater stress-resilience may lead to down-regulation of the inflammatory response by counteracting the neuroendocrine reaction to stressful events (Brydon *et al*., 2009). Furthermore, it is also possible that chronic low-grade inflammation lowers the level of dispositional optimism. In a recent cross-sectional study among middle-aged healthy adults (n=6814) circulating levels of C-reactive protein (CRP) (Roy *et al*., 2010), a non-specific systemic inflammatory acute-phase protein, were inversely associated with higher dispositional optimism scores. However, the cross-sectional nature of the reported association between inflammation and optimism does not allow drawing *conclusions* about causal pathways. It remains unclear whether low levels of optimism are secondary to inflammation, or low inflammatory markers are secondary to optimism, or whether a third factor is involved in the putative association.

It is well-known that (abdominal) obesity is strongly related to inflammation and may therefore act as a potential moderator of the association between inflammation and dispositional optimism. Visceral fat is an important determinant of moderately increased CRP levels in both men and women (Visser *et al*., 1999). Furthermore, weight changes have been correlated to changes in CRP levels (Festa *et al*., 2001; Tchernof *et al*., 2002). In an earlier study, a gene/environment interaction was reported for the effect of body mass index (BMI) on CRP plasma levels (Eiriksdottir *et al*., 2009). In obese subjects, a stronger association was found between the CRP single nucleotide polymorphism (SNP) rs1205 and plasma CRP levels than in lean subjects, especially in men.

Mendelian randomization is being used to investigate biological relationships by inferring causality when unobserved confounding is likely (Lawlor *et al*., 2008; Smith & Ebrahim, 2004; Bochud & Rousson, 2010). This approach is based on the random allocation of alleles at the moment of gamete formation and can be considered a natural form of a randomized controlled trial (Sheehan *et al*., 2008). Previous studies using Mendelian randomization have shown that CRP transcription and plasma concentrations depend on genetic variation at single nucleotide polymorphisms (SNPs): rs2808628, rs2808630, rs1205, rs1800947, rs1417938, and rs3091244 (Lange *et al*., 2006; Carlson *et al*., 2005; Crawford *et al*., 2006; Szalai *et al*., 2002; Hage & Szalai, 2007; Kathiresan *et al*., 2006; Bos *et al*., 2008).

Furthermore, a recent Mendelian randomization study showed that the observed association between CRP and BMI is most likely driven by BMI, with CRP being raised due to obesity (Timpson *et al.*, 2010). Regarding affective states, the relationship with CRP genetic variation has only been studied for depressive symptoms, with negative findings in two previous cross-sectional studies among 868 middle-aged subjects and 3700 community-dwelling elderly subjects (Halder *et al.*, 2010; Almeida *et al.*, 2009). The relationship between CRP genotype and the positive affective trait dispositional optimism remains largely unexplored.

The present study investigates the associations between CRP haplotypes and dispositional optimism in three different samples of older subjects. We hypothesized that CRP haplotypes associated with higher levels of CRP in plasma may also contribute to lower levels of dispositional optimism. Since obesity is strongly related to inflammation and may modulate the association between CRP haplotypes and CRP plasma levels (Eiriksdottir *et al.*, 2009), we also investigated the effect of BMI on the association between CRP haplotypes and dispositional optimism by repeating the analyses stratifying for BMI.

Methods

Study sample

The present study uses data from participants of the Arnhem Elderly Study (AES), the Leiden Longevity Study (LLS), and the Zutphen Elderly Study (ZES). The study design and population characteristics of these three samples have been described in detail elsewhere (Feskens *et al.*, 1993; Schoenmaker *et al.*, 2006; van den Hombergh *et al.*, 1995). The AES is a population-based study among 685 non-institutionalized adults who agreed to undergo venipuncture (aged 65-84 years) to investigate lifestyle and health characteristics (Giltay *et al.*, 2004b). In the LLS, 420 families with long-lived Caucasian siblings, together with their offspring and the offspring's partners, were recruited to study predictors and mechanisms in

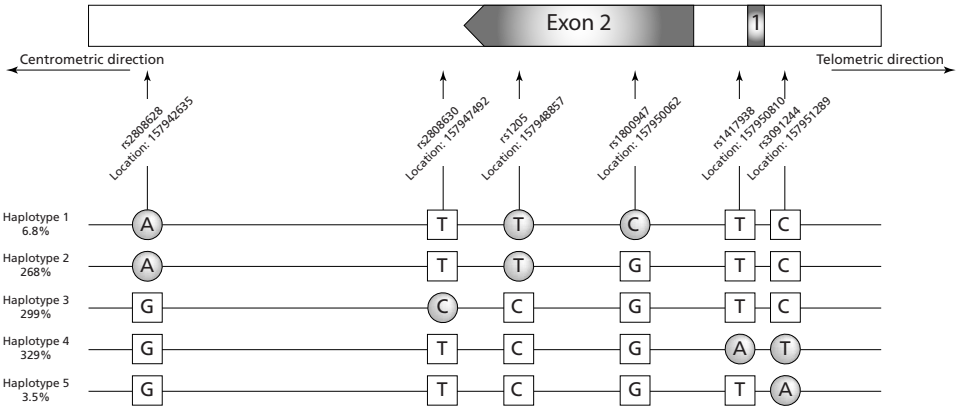

Figure 1. Schematic overview of the structure of the C-reactive protein gene, consisting of 2 exons separated by a single intron. The orientation of the gene is marked by arrows, with the gene transcribed from left to right. Arrows mark the approximate location of the 6 single nucleotide polymorphisms that are in close linkage disequilibrium. The five most frequent haplotypes are presented, which were similar to those found in populations from Northern and Western European ancestry. Note that the percentages do not sum up to 100% because infrequent haplotypes were not taken into account.

longevity. Families were eligible for the study if at least two long-lived, full siblings were alive, where men were considered to be long-lived if they were 89 years or older and women if they were 91 years or older (Schoenmaker *et al*., 2006). The ZES is a longitudinal investigation of risk factors for chronic diseases among Caucasian men (aged 65-84 years), of whom 560 participated in 1990 (Feskens *et al*., 1993). Participants of the three samples were included in subsequent analysis when having complete data on CRP plasma concentrations, dispositional optimism scores, and at least four of the six CRP SNPs. In a number of subjects DNA was not available. This selection criterion resulted in a final study sample of 1084 participants: 426 Caucasian subjects aged 65-85 years from the AES, 355 Caucasian subjects aged 60-84 years from the LLS, and 303 Caucasian subjects aged 70-89 years from the ZES. All studies were conducted in compliance with the principles of the Helsinki Accord and were approved by the local ethics committees. Standard informed consent was obtained from all participants.

Plasma CRP measurement and CRP SNPs genotyping

Blood samples were drawn with standard venipuncture techniques. Plasma CRP was assayed with a highly sensitive enzyme-linked immunosorbent assay procedure in the AES and with automated enzymatic colorimetric *methods* using a Modular P analyzer (Roche, Switzerland) in the LLS. CRP plasma levels were not measured in the ZES and therefore CRP levels were available in 781 (72%) of 1084 subjects.

Genomic DNA was isolated from the blood samples according to standard procedures. SNPs at the CRP gene were determined together with the frequency of six well-characterized CRP polymorphisms that showed to be related with plasma CRP levels (Figure 1). I-plex assays were assigned using Assay designer software (Sequenom). Genotyping was performed using the MassArray platform according to the manufacturer's protocols (Sequenom, San Diego, CA). After PCR on 2.5 ng of DNA, a primer extension reaction was performed to introduce mass differences between alleles. After removing salts by adding a resin, ~15 nL of the product was spotted onto a target chip with 384 patches containing matrix. Mass differences were detected using the Brucker Autoflex MALDI-TOF mass spectrometer, and genotypes were assigned real-time user Typer 3.1 software (Sequenom). Genotype frequencies of these SNPs showed no significant deviations from the Hardy-Weinberg equilibrium (all p-values>0.05, except for the SNP rs3091244 in the ZES with a p=0.03).

The haplotype frequencies were generated using SNPHAP (Clayton, 2002; version 1.3; available online at http://www-gene.cimr.cam.ac.uk/clayton/software/) with an estimation-maximization algorithm. Six SNPs (i.e. rs2808628, rs2808630, rs1205, rs1800947, rs1417938, and rs3091244) were used to generate five common haplotypes that determine about 10% of the inter-individual variability in CRP levels in the absence of infection (Hage & Szalai, 2007; Lange *et al*., 2006). Haplotypes with prevalences larger than 3% were selected for further comparison and named haplotype 1, haplotype 2, haplotype 3, haplotype 4, and haplotype 5. Haplotypes were placed in the numerical order known to be associated with increasing plasma CRP levels (Carlson *et al*., 2005; Bos *et al*., 2008).

Dispositional optimism

Dispositional optimism was assessed using the Dutch Scale for Subjective Well-being for Older persons (SSWO) in 426 participants from the AES (Tempelman, 1987), with the Life Orientation Test-Revised (LOT-R) in 355 participants from the LLS (Scheier *et al*., 1994), and with the 4-item optimism questionnaire (4Q) in 303 participants from the ZES (Giltay *et al*., 2006). The SSWO consists of 30 items rated on a 3-point scale divided into five sub-

scales; including an optimism subscale composed of seven items (Giltay *et al.*, 2004a). Within the seven items yielding an optimism score, one item required reversed coding. A typical item was: "I still expect much from life". The total score ranges from 0-14 points (Giltay *et al.*, 2004a; Tempelman, 1987; Giltay *et al.*, 2004b; Tempelman, 1987). The LOT-R consists of 10 items rated on a 5-point Likert scale, with six items yielding an optimism score and four filler items (Scheier *et al.*, 1994). Within the six score items, three negatively stated items required reversed coding. A typical questionnaire item was: "Overall, I expect more good things to happen to me than bad things". The total LOT-R score ranges from 0-24 points. The 4Q (Giltay *et al.*, 2006) consists of four statements rated on a 3-point Likert scale, such as "I am still full of plans". Within the four score items, two negatively stated items required reversed coding. The additional answer category "do not know" was coded as the midpoint (score 1). The total score ranges from 0-8 points. For the computation of the optimism scores, one missing item per subject was allowed, being subsequently imputed with the mean of the remaining seven, five, or three items for the SSWO, the LOT-R, and the 4Q, respectively. Higher scores on all three optimism scales were indicative of higher optimism levels. Similar indices of moderate internal consistency were found for the three optimism scales (with Cronbach's alpha's: SSWO= 0.76, LOT-R= 0.67, and 4Q=0.65).

Other variables

Sociodemographic and lifestyle characteristics were obtained from all participants, including age and gender. Marital status was dichotomized as being married or not. Smoking status was classified as no smoking, former smoking, and current smoking. Alcohol use was dichotomized as current alcohol consumption or no alcohol consumption. BMI was calculated from the measured weight and height and two strata were formed according to the cut off of 25 kg/m^2. A history of cancer and a history of cardiovascular disease (i.e. heart failure, myocardial infarction, or stroke) were also dichotomized.

Statistical analysis

Sociodemographic and lifestyle characteristics were summarized using descriptive statistics. Differences across the three studies were analyzed using chi-square tests and one-way analysis of variance (ANOVA), when appropriate. Results are presented as numbers and percentages for categorical variables, means and standard deviations for continuous normally distributed variables, and medians with interquartile ranges for continuous skewed variables. Logarithmic transformation was applied to normalize distributions of the positively skewed CRP values and subsequent analyses were conducted on these transformed values. Back-transformed geometric mean values are presented in all tables. To enable comparison of the optimism scores obtained by three different scales, z-scores (i.e. standardized scores) were used.

First, one-way ANOVAs were used to assess the associations between the alleles of the six SNPs and dispositional optimism within each sample. Given the low frequency of the minor allele of the SNP rs1800947, the alleles GC/CC were pooled into one group.

Second, univariate ANOVAs were used to study the association between CRP haplotypes and circulating CRP. The same analyses were used to investigate the relationship between CRP haplotypes and dispositional optimism. In each analysis, the association was subsequently tested adjusting for potential confounders, including age, gender, marital status, smoking status, alcohol use, a history of cancer or cardiovascular disease, and cohort (when appropriate). Finally, to assess the effect modification of obesity on the association between CRP haplotypes and CRP plasma levels or dispositional optimism, we stratified according

to BMI group (i.e. group 1 had a BMI <25 kg/m^2, group 2 had a BMI ≥25 kg/m^2) (Sweat *et al.*, 2008). Linear regression analyses (weighted for haplotype probability) were used to test for linear trend over the haplotypes ordered according to increasing CRP levels. Finally, to unveil potential differences between men and women, the same analyses were repeated testing the interaction with gender.

All p-values are two-tailed and considered statistically significant at the level of p <0.05. Data analyses were performed using SPSS for Windows, version 17.0 (Chicago, IL).

Results

Sociodemographic characteristics

Sociodemographic and lifestyle characteristics are summarized in Table 1. The mean age of the study sample was 71 (SD 7) years. The percentage of male participants was around 45% in the AES and the LLS, whereas the ZES study was solely composed of men. Participants of the AES more frequently reported a history of cardiovascular disease. Finally, median levels of circulating CRP were similar across the two studies with available data (i.e. AES and LLS) and a positive association between serum CRP levels and BMI (adjusted beta= 0.35; p<0.001) was found.

CRP genotype and CRP levels

Figure 1 presents the five haplotypes used in this study, with prevalence rates highly consistent with those found in populations with a northern/western European origin (Bos *et al.*, 2008; Brull *et al.*, 2003; Russell *et al.*, 2004). Genetic variation at these chromosomal regions is represented by so-called tag SNPs (also depicted in Figure 1). As expected, results from the linear regression analysis showed that CRP haplotypes were associated with increasing CRP plasma levels (beta=0.088; p=0.001) in the combined study sample. In the multivariable model, this association persisted (beta=0.094; p<0.001). Largely similar results were found

Table 1. Sociodemographic and clinical characteristics of the 1084 participants.

	Total (n=1084)	ZES (n= 303)	AES (n= 426)	LLS (n= 355)
Age (years), mean ± SD	70.7 ± 6.6	70.6 ± 4.3	74.3 ± 5.7	66.2 ± 4.5
Male, n (%)	698 (64.4%)	303 (100%)	205 (47.9%)	192 (54.1%)
Married, n (%)	864 (80.4%)	265 (89.8%)	260 (60.7%)	339 (95.8%)
Current smoker, n (%)	220 (20.3%)	80 (26.4%)	97 (22.7%)	44 (12.5%)
Alcohol use, n (%)	760 (70.1%)	230 (78.5%)	266 (70.2%)	265 (75.3%)
Cardiovascular disease, n (%)	161 (15.4%)	35 (11.6%)	100 (23.6%)	26 (8.2%)
Cancer, n (%)	61 (5.8%)	17 (5.6%)	18 (4.2%)	26 (8.3%)
Body mass index, mean ± SD (kg/m^2)	25.8 ± 3.7	25.6 ± 2.8	25.9 ± 3.9	25.8 ± 3.5
Body mass index ≥25kg/ m^2	595 (54.9%)	172 (56.8%)	228 (53.5%)	195 (54.9%)
C-reactive protein, median (p25; p75)	1.80 (0.90; 3.60)	–	2.30 (1.18; 4.10)	1.40 (0.74; 2.86)

ZES: Zutphen Elderly Study; AES: Arnhem Elderly Study; LLS: Leiden Longevity Study; SD, standard deviation.

Table 2. Associations between common C-reactive protein (CRP) haplotypes, plasma CRP levels and dispositional optimism in 1084 participants.

		Dispositional optimism							
		AES		LLS		ZES		Overall	
Haplotype	Genotype combination	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)	n	Mean (SE)
Crude:									
1	ATTCTC	28	−0.14 (0.13)	27	−0.03 (0.13)	18	−0.16 (0.15)	47	−0.10 (0.08)
2	ATTGTC	115	0.19 (0.07)	90	−0.07 (0.07)	79	−0.25 (0.07)	177	−0.01 (0.04)
3	GCCGTC	131	−0.06 (0.06)	103	−0.07 (0.07)	79	−0.11 (0.07)	203	−0.07 (0.04)
4	GTCGAT	126	−0.08 (0.06)	115	−0.01 (0.06)	108	−0.14 (0.06)	216	−0.07 (0.04)
5	GTCGTA	17	−0.10 (0.17)	9	−0.14 (0.23)	12	0.05 (0.26)	22	−0.08 (0.12)
		Beta=−0.066; p=0.057		Beta=0.012; p=0.76		Beta= 0.045; p=0.27		p=0.55	
Adjusted*:									
1	ATTCTC	24	−0.18 (0.14)	23	−0.09 (0.15)	17	−0.09 (0.16)	64	−0.12 (0.09)
2	ATTGTC	100	0.16 (0.07)	79	−0.06 (0.08)	77	−0.23 (0.07)	254	−0.02 (0.04)
3	GCCGTC	113	−0.04 (0.06)	93	−0.08 (0.07)	73	−0.11 (0.07)	276	−0.07 (0.04)
4	GTCGAT	115	−0.12 (0.06)	102	−0.02 (0.07)	104	−0.12 (0.06)	320	−0.09 (0.04)
5	GTCGTA	14	−0.20 (0.18)	8	−0.03 (0.25)	12	0.07 (0.25)	33	−0.12 (0.13)
		Beta=−0.072; p=0.047		Beta= 0.019; p=0.63		Beta= 0.039; p=0.35		p=0.45	

Five common haplotypes were constructed from rs2808628, rs2808630, rs1205, rs1800947, rs1417938, and rs3091244.
***Geometric estimated means adjusted for age, gender, marital status, smoking status, alcohol use, history of cancer or cardiovascular disease, and cohort (when appropriate) with standard errors (SE) are presented for dispositional optimism.**
Weighted linear regression analysis was used to test for linear trend over the five haplotypes.

when studying the association within samples. After stratification for BMI, the adjusted association between CRP haplotypes and increasing levels of circulating CRP only persisted in the obese group (beta=0.112; p=0.002), but disappeared in the non-obese group (beta=0.069; p=0.08) (Figure 2). The difference in strength of the associations across the obesity groups was significant after adjustment for marital status, age, gender, alcohol, smoking habits, cardiovascular disease, cancer, and cohort.

CRP and dispositional optimism

There was an inverse association between serum CRP levels and dispositional optimism (beta=−0.053; p=0.03). However, this association disappeared after adjustment for the following confounders: age, gender, marital status, smoking status, alcohol use, and a history of cancer or cardiovascular disease (beta=−0.006; p=0.83).

Table 2 presents results on the association between CRP haplotypes and dispositional optimism. No significant overall association was found between CRP haplotypes and levels of dispositional optimism in the combined sample. However, a marginal significant association was found in the AES after adjusting for potential confounders. After stratification for BMI, an association was found between CRP haplotypes and dispositional optimism (z-scores) in the overweight/obese group (n=595; beta=−0.068; p=0.03), but not in the non-obese group (n=489; beta=0.049; p=0.15) (Figure 2). The difference in strength of the associations across the obesity groups was significant after adjustment for marital status, age, gender, alcohol, smoking habits, cardiovascular disease, cancer, and cohort (p for interaction term "haplotype* optimism" was 0.04). Associations between CRP haplotypes and dispositional optimism in obese subjects were of similar strength in obese men (beta =− 0.070) and obese women (beta =− 0.067), and the interaction term with gender was not statistically significant.

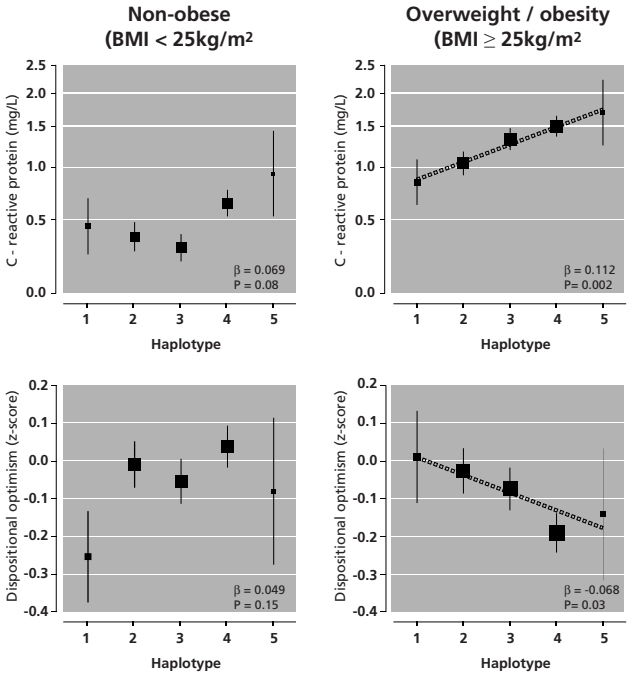

Figure 2. The main standard scores (with error bars repesenting standard errors) for C-reactive protein (CRP) levels according to the CRP gene haptotypes. The 5 common haptotypes were constructed from rs2808628, rs2808630, rs1205, rs1800947, rs1417938 and rs3091244. The size of each square is proportional to the number of measurements. Scores are adjusted for age, gender (2 catagories), smoking status (3 catagories), alcohol use (2 catagories), prevelent cancer (2 catagories), prevalent cardiovasculair disease (2 catagories), and cohort (3 catagories). P-values are for linear trend (by weighted regression analyses) over increasing haptotypes.

Discussion

The present study aimed to determine whether specific haplotypes of the CRP gene known to affect gene transcription and circulating levels of CRP (Bos *et al.*, 2008; Carlson *et al.*, 2005; Crawford *et al.*, 2006; Hage & Szalai, 2007; Kathiresan *et al.*, 2006; Lange *et al.*, 2006; Szalai *et al.*, 2002; Brull *et al.*, 2003; Russell *et al.*, 2004), were also associated with dispositional optimism. The association between C-reactive protein (CRP) and low dispositional optimism was tested using a Mendelian randomization design. There was an association between CRP genotype and circulating serum CRP levels. However, no association was found between CRP genotype and low optimism, implying that a causal association is unlikely. The lack of relationship suggests that reverse causation, bias, or confounding generated the link between high CRP plasma levels and low optimism. Our data indicated that BMI was a likely confounder of the relationship, as subjects with a higher BMI displayed higher CRP levels and lower optimism. Since previous studies had reported a gene/environment interaction for the relationship between BMI and CRP levels (Eiriksdottir *et al.*, 2009), we performed extra stratified analyses for BMI. BMI modulated the association between CRP haplotypes and dispositonal optimism, as an inverse association was only found in the obese group.

Although our findings are interesting and merit further investigation, some study limitations need addressing. First, three different instruments were used to measure dispositional optimism. Second, it should be noted that about a 25% of the LLS were sibling pairs, and therefore not genetically independent. Third, although we included three cohorts in the analyses, the total number of 1084 participants is relatively small for a genetic association study. Finally, we restricted our analysis to Caucasian European subjects, which limits the generalization of our findings to non-Caucasian populations. Given the evidence that circulating

levels of CRP are higher in African Americans than European Caucasians (Carlson *et al.*, 2005; Lange *et al.*, 2006), further research in non-Caucasian populations may be needed.

Our results are in line with the findings of a cross-sectional MESA (Multi-Ethnic Study of Atherosclerosis) study among 6184 middle-aged adults, which showed that higher scores in the LOT-R were inversely associated with serum CRP levels (Roy *et al.*, 2010). Similar to the present study, this association attenuated after adjustment for sociodemographic and life-style-related factors, including BMI. Similarly, our results concur with findings from other cross-sectional studies investigating positive affect, a construct closely related to optimism (Steptoe *et al.*, 2005; Janicki-Deverts *et al.*, 2007; Steptoe *et al.*, 2008). We have extended their findings by investigating the role of allelic variation at the CRP gene and by exploring the modifying effect of obesity on the association between the CRP gene and both CRP levels and dispositional optimism. We found that the association between CRP haplotypes and CRP levels was stronger in subjects with obesity. This confirms findings of another study (among 2296 older subjects) reporting that the association between the minor allele of the CRP SNP rs1205 and higher CRP levels was also stronger in subjects with higher BMI (Eiriksdottir *et al.*, 2009). Likewise, in another study, CRP was related to poorer cognition in women with a BMI higher than 25 kg/m2, but not in leaner women (Sweat *et al.*, 2008). We found that CRP haplotypes were associated with dispositional optimism when the BMI was higher than 25 kg/m2; this suggests that high CRP levels are associated with lower optimism, but only in obese subjects.

It is well-known that the volume and distribution of adipose tissue are critical in the production of CRP-inducing factors (Timpson *et al.*, 2010; Fried *et al.*, 1998; Visser *et al.*, 1999). One of these factors is the IL-6, a cytokine produced by adipose tissue that regulates the hepatic synthesis of CRP (Bastard *et al.*, 1999). Since this pro-inflammatory cytokine is also associated with positive affect (Janicki-Deverts *et al.*, 2007), it is worthwhile to study both IL-6 and CRP in relation to optimism in obese and non-obese subjects, as the interaction of many other pro-inflammatory proteins (e.g. tumor necrosis factor-α [TNF-α]) with obesity is complex.

Although the Mendelian randomization design makes it less likely, we cannot exclude inverse causation as a possible explanation for our findings, i.e. that dispositional optimism may affect systemic inflammation rather than vice versa. Dispositional optimism is associated with health-promoting behaviors such as non-smoking, increased physical activity, moderate alcohol consumption, and more fruits, vegetables and whole grains in the diet (Giltay *et al.*, 2007). Therefore, the association between dispositional optimism and inflammation levels might be moderated through longstanding changes in health behaviours and lifestyle, such as healthy diets and weight reduction. Dispositional optimism is associated with a greater resilience against stress which, in turn, may reduce the affective reaction to a stressful event. Otherwise, poor coping strategies result in a continued and enhanced activation of the hypothalamic-pituitary-adrenal (HPA) axis, inducing a cascade of neuroendocrine and hormonal changes (Hayley *et al.*, 2005). Thus, chronic dysregulation of the HPA axis may also contribute to inflammatory processes. By favouring more benign appraisals of stress, optimism may lead to a downregulation of the neurendocrine system and, thereby, to decreased levels of inflammatory cytokines and acute-phase proteins (Brydon *et al.*, 2009). Nevertheless, under conditions of acute biological or psychological stressors, optimism may help to boost inflammatory processes favouring a more rapid and successful response to the stressor. For example, in a study among 18 healthy older adults, those with higher levels of optimism showed greater in vitro IL-2 and interferon-γ responses to viral stimulation (Costanzo *et al.*, 2004).

In summary, our study indicates that allelic variation at the CRP gene is related to CRP levels and dispositional optimism, and that the strength of this association is modulated by BMI. Further prospective studies are necessary to confirm our findings. Such studies could investigate the role of BMI in the association between inflammation and affective states that also incorporate other markers of inflammation, such as IL-6 or TNF-α.

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Chapter 5

Physical activity after myocardial infarction: is it related to mental health?

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Nathaly Rius-Ottenheim
Johanna M Geleijnse
Daan Kromhout
Roos C van der Mast
Frans G Zitman
Erik J Giltay

Abstract

Background Physical inactivity and poor mental well-being are associated with poorer prognoses in patients with cardiovascular disease. We aimed to analyze the cross-sectional and prospective associations between physical activity and mental well-being in patients with a history of myocardial infarction.
Design Longitudinal, observational study.
Methods 600 older subjects with a history of myocardial infarction (age range 60-80 years) who participated in the Alpha Omega Trial (AOT) were tested twice at baseline and at 40 months follow-up for physical activity (with the Physical Activity Scale for the Elderly [PASE]), depressive symptoms (with the Geriatric Depression Scale [GDS-15]), and dispositional optimism (with the Life Orientation Test [LOT-R]). Linear (multilevel) and logistic regression analyses were used to examine cross-sectional and longitudinal associations.
Results Physical activity was cross-sectionally associated with depressive symptoms (adjusted beta=−0.143; p= 0.001), but not with dispositional optimism (adjusted beta=0.074; p=0.07). We found a synchrony of change between physical activity and depressive symptoms (adjusted beta=−0.155; p<0.001), but not with dispositional optimism (adjusted beta=0.049; p=0.24). Baseline physical activity did not predict depressive symptoms at 40 months of follow-up.
Conclusions Concordant inverse associations were observed for (changes) in physical activity and depressive symptoms. Physical activity did not predict depressive symptoms or low optimism.

Introduction

Physical activity is thought to confer benefits on mental health in older adults (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991; Lampinen, Heikkinen, Kauppinen, & Heikkinen, 2006; Strawbridge, Deleger, Roberts, & Kaplan, 2002). It has been shown that older adults who engage in regular physical activities are less likely to have depressive symptoms and are more optimistic than their less physically active peers (Camacho et al., 1991; Giltay, Geleijnse, Zitman, Buijsse, & Kromhout, 2007). Conversely, the combination of physical inactivity with depressive symptoms and low optimism increases the risk of cardiovascular morbidity and mortality in patients with a history of myocardial infarction (Lett et al., 2004; Frasure-Smith et al., 2009; Davidson, Mostofsky, & Whang, 2010; Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004; Netz, Wu, Becker, & Tenenbaum, 2005). Therefore, a better understanding of the relationship between physical activity and mental health is of particular importance in older patients with cardiovascular disease (Donker, 2000).

Several cross-sectional, population-based studies have shown an inverse association between physical activity and depressive symptoms (Conn, 2010; Camacho et al., 1991; Strohle, 2009; Teychenne, Ball, & Salmon, 2008; Sanchez-Villegas et al., 2008; Jonsdottir, Rodjer, Hadzibajramovic, Borjesson, & Ahlborg, 2010). However, the longitudinal relationship between physical activity and depressive symptoms has been less extensively investigated and the results have been inconsistent. While some previous prospective studies found evidence of a predictive effect of physical inactivity on depressive symptoms (Camacho et al., 1991; Farmer et al., 1988; Wise, Adams-Campbell, Palmer, & Rosenberg, 2006), others did not (Cooper-Patrick, Ford, Mead, Chang, & Klag, 1997; Kritz-Silverstein, Barrett-Connor, & Corbeau, 2001; Weyerer, 1992). These inconsistencies may be explained by other factors such as the presence of depressive symptoms at baseline being a stronger determinant for future depressive symptoms than physical inactivity (Lampinen et al., 2006). Only two studies have described an inverse longitudinal relationship between baseline physical activity and depressive symptoms among community-dwelling adults free of depressive symptoms at baseline (Camacho et al., 1991; Farmer et al., 1988). However, both studies measured physical activity with a single self-report global question, instead of a validated tool that incorporated a broad range of activities (Macera et al., 2001; Sternfeld, Cauley, Harlow, Liu, & e, 2000).

The association between physical activity and depressive symptoms has been less well investigated in patients with cardiovascular disease In a study among 189 patients with history of acute myocardial infarction (MI), coronary bypass surgery, or a percutaneous coronary intervention, an inverse association was found between participation in an exercise training and prevalence of depressive symptoms (i.e. reduction of 40% of depressive symptoms in the intervention group). Furthermore, both exercise and depressive symptoms were longitudinally associated with survival (Milani, Lavie, Mehra, & Ventura, 2011). Similarly, in a recent study among 5888 ambulatory patients with CHD (defined as angina, previous MI or coronary revascularization) an odds ratio of 3.4 was reported for the lowest physical activity group regarding their risk for depressive symptoms. Both studies found that physical inactivity and depressive symptoms were partly independent predictors of cardiovascular mortality (Win et al., 2011; Milani et al., 2011).

Physical activity has not only been related to the state-like depressive symptoms, but also to positive psychological traits (Gauvin & Spence, 1996; Reed & Ones, 2006; Scully, Kremer, Meade, Graham, & Dudgeon, 1998; Baruth et al., 2011; Stubbe, de Moor, Boomsma, & de Geus, 2007). Dispositional optimism refers to one's generalized positive expectations

towards the future (Carver, Scheier, & Segerstrom, 2010; Scheier, Carver, & Bridges, 1994a). People with high dispositional optimism tend to expect good things rather than bad things to happen in their future. On the contrary, people with depressive symptoms incline to anticipate negative outcomes of life challenges and have the perception that these situations are unchangeable and uncontrollable. These perceptions of lack of control on a stressor are linked to learned helplessness (Maier & Seligman, 1976). The differences in the way that we see our future are thought to greatly influence our behavior and our health. Dispositional optimism may protect against the development of depressive symptoms (Giltay, Zitman, & Kromhout, 2006). Furthermore, dispositional optimism reduces cardiovascular risk in community dwelling elderly subjects (Giltay, Kamphuis, Kalmijn, Zitman, & Kromhout, 2006; Giltay et al., 2004). It has been hypothesized that dispositional optimism reduces cardiovascular risk by influencing lifestyle, including physical activity (Kavussanu & McAuley, 1995; Giltay et al., 2007).In a study among 773 community-dwelling older men, higher optimism was strongly associated with higher levels of physical activity (Giltay et al., 2007). The longitudinal relationship between physical activity and optimism remains largely unexplored. Nevertheless, an observational study with a follow-up of only one week found a positive association between physical activity and positive affect(Mata et al., 2011), an affective state that is related to optimism in the same way depression is related to neuroticism.

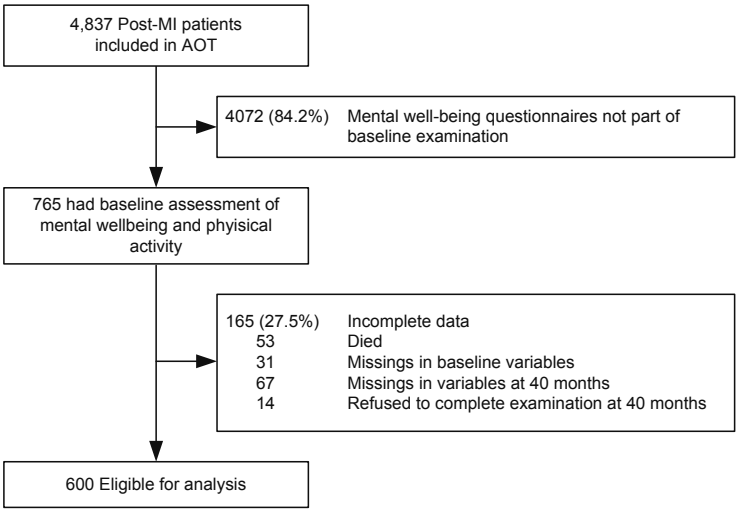
In the present study, data from the Alpha Omega Trial (AOT) (Kromhout, Giltay, & Geleijnse, 2010) were used to examine, both cross-sectionally and longitudinally, the potential associations of physical activity with depressive symptoms and dispositional optimism. We aimed to assess (a) whether physical activity was associated with depressive symptoms and dispositional optimism; (b) whether or not changes in physical activity were associated with changes in depressive symptoms and dispositional optimism (i.e. synchrony of change); and (c) to investigate the prospective association of baseline low physical activity with depressive symptoms and low optimism over time.

Methods

Study sample

Participants were recruited as part of the Alpha Omega Trial, a randomized, double-blind controlled trial that investigated the effects of n-3 fatty acids on relapse of cardiovascular disease in a sample of elderly subjects with a history of myocardial infarction. Post-MI patients were recruited by cardiologists from 32 hospitals between 2002 and 2006, and the date of final follow-up was December 23rd, 2009. Subjects were considered eligible for the trial if they were aged between 60 to 80 years, if they had a verified diagnosed myocardial infarction up to 10 years before randomization, were not cognitively impaired (i.e. MMSE score ≥22points), and were willing to provide written informed consent (Geleijnse et al., 2010; Kromhout et al., 2010). These selection criteria resulted in a sample of 4837 eligible subjects who were subsequently randomized into the following four groups of n-3 fatty acids: a combination of eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA); alpha-linolenic acid (ALA); a combination of EPA, DHA, and ALA; or placebo. Of the 4837 participants included in the initial sample, 765 participants completed baseline questionnaires on physical activity, depressive symptoms, and dispositional optimism. During follow-up, 53 participants died, 14 participants refused further participation in the study, and 31 participants had missing values on the covariates included in the present analysis. This resulted in a sample of 667 participants at the end of the follow-up. Of the 667 remaining participants, 67 had

missing values on the covariates at the end of the follow-up. Thus, the final sample used for the present analysis comprised 600 participants (Figure 1). The trial was conducted in compliance with the Declaration of Helsinki and approved by the Medical Ethics Committee of South-West Holland and by the ethics committees of all participating hospitals. Written informed consent was obtained from all participants.



Physical activity

Physical activity was assessed using the Physical Activity Scale for the Elderly (PASE), a validated brief self-report questionnaire designed to measure the level of self-reported physical activity in individuals aged 65 years or older (Schuit, Schouten, Westerterp, & Saris, 1997; Washburn, McAuley, Katula, Mihalko, & Boileau, 1999). This scale comprises 12 items regarding occupational, household, and leisure activities during the previous week to the assessment. The total PASE score is calculated by multiplying duration of activity (hours per week) or participation in an activity (yes/no) by empirically derived weight, daily energy expenditures (metabolic equivalents of task [MET]) and self-reported physical activity, and then summing the product for all 12 items. In our analyses, we also used the continuous measure of physical activity MET hours per week. One MET is the equivalent to the rate of energy consumption of a person at rest (e.g. sitting quietly for 1 hour).

Psychometric assessment

Depressive symptoms at baseline and during follow-up were assessed with the 15-item version of the Geriatric Depression Scale (GDS-15). The GDS-15 is a validated self-report instrument designed to assess depressive symptoms in older people (de Craen, Heeren, & Gussekloo, 2003). This instrument is especially useful to measure depressive symptoms in older patients with cardiovascular disease, as it excludes somatic symptoms that might also be related to physical illnesses rather than to depressive symptoms (Yesavage et al., 1982). The total score ranges from 0 to 15 points, with higher scores indicating more depressive symptoms. For the computation of the GDS-15 score, two missing items were allowed, being subsequently imputed with the mean of the remaining items. The Cronbach's alpha was 0.77.

Dispositional optimism was assessed using the Life Orientation Test Revised (LOT–R). The LOT–R is a 10-item self-report questionnaire with six items that yield an optimism score and four filler items (Scheier, Carver, & Bridges, 1994b). The scale included three negatively stated items which required reversed coding before total score computation. Subjects were asked to express the extent of their agreement with each of the items, coding their responses on a 5-point Likert type scale. The LOT-R score ranges from 0-24, with higher scores being indicative for higher optimism levels. For the computation of the optimism scores, one missing item per subject was allowed, being subsequently imputed with the mean of the remaining items. The Cronbach's alpha was 0.57.

Covariates

At baseline, data were collected on demographic factors, lifestyle, medical history, current health status, and medication use. Information about the highest attained level of education was used as an indicator of socioeconomic status, with more than 11 years of education as the upper category. Marital status was dichotomized into the categories being married (or cohabiting) or not (i.e. unmarried, divorced, widow). Smoking habits were categorized into never smoked, smoked in the past, and current smoking. Alcohol use was categorized into no alcohol use, use of 1 to 13 alcohol units per week, and use of more than 14 alcohol units per week. Body mass index (BMI) was calculated from the measured weight and height. Reported self-rated health was dichotomized into excellent to good self-rated health and moderate to poor self-rated health. Treatment group represents the randomized groups that received one of the following interventions: administration of a combination of the n-3 fatty acids EPA and DHA; administration of ALA; administration of a combination of ALA, EPA and DHA; or administration of placebo (Kromhout et al., 2010). Cognitive function was measured with the Mini Mental State Examination (MMSE) and was included in the multivariable analyses as a continuous variable.

Statistical analyses

Sociodemographic and baseline characteristics were summarized using descriptive statistics. Categorical variables were presented as proportions. Continuous data were presented as mean (standard deviation) or as median (interquartile ranges), when appropriate. If the criteria of normality were not met (i.e. depressive symptoms and physical activity), log-transformed values were used to improve their distributions.

Because the two observations (i.e. baseline and at 40 months) were not independent, multilevel regression analyses (i.e. linear mixed models) with an unstructured covariance matrix were used to investigate the cross-sectional associations of physical activity with depressive symptoms and dispositional optimism. Associations were first assessed in a crude model. Subsequently, we repeated the linear regression analyses adjusting first for age and gender (Model 1) and then additionally adjusting for education, marital status, smoking habits, alcohol use, body mass index, MMSE score, treatment group, diabetes mellitus, stroke at baseline, and time since last MI (Model 2). Data are presented as standardized beta coefficients.

Linear regression analyses were used to analyze the temporal associations of absolute changes (i.e. delta) in physical activity with absolute changes in depressive symptoms and dispositional optimism scores in univariate and multivariable models, as described in the previous paragraph. Data are presented as standardized beta coefficients.

Logistic regression analyses were conducted to examine the predictive effect of physical activity and depressive symptoms in both in univariate and multivariable models. To this purpose, we dichotomized the variables "physical activity", "depressive symptoms", and

"low optimism". Moderate and/or vigorous physical activity was defined as "physical activity lasting more than 30 minutes, during at least 5 days per week, with energy expenditure higher than 3 METs" (Pate et al., 1995). Presence of depressive symptoms was defined as a score higher or equal to 4 points on the GDS-15 . This cut-off has shown to have a specificity of 76% in a previous study with older persons (de Craen et al., 2003). Low optimism was defined as a score lower than 12 points on the LOT-R. This cut-off has been less well investigated, but earlier studies of our group using the same sample showed that this cut-off represented 20% of the subjects with the lowest scores (van de Rest et al., 2010). Furthermore, we excluded from the analyses the subjects with depressive symptoms at baseline, as defined by a GDS score ≥4 points, (n=155, 25.8%) and low optimism at baseline, as defined by a LOT-R score < 12 points, (n=107, 17.8%).

All tests were two-tailed with $p<0.05$ denoting statistically significance. The software used was SPSS version 17.0 (SPSS Inc., Chicago, Ill).

Results

Cross-sectional results

Table 1 shows the sociodemographic and health characteristics of the 600 participants of the Alpha Omega Trial with complete data for the main outcome variables. The included subjects had a mean age of 68.5 years and were predominantly male (81%). Most participants were married and had a low educational level. The median baseline MMSE score was 27 points. The mean BMI was 27 kg/m2 and more than one fifth of the participants fulfilled the criterion of obesity (i.e. BMI ≥30 kg/m2). The mean time elapsed since the last MI was 3.9 years. After 40 months of follow-up, there was a decrease in the number of married participants and a decrease in the number of subjects who reported drinking more than 14 alcohol units per week. There were 10 participants who initiated antidepressants during follow-up, whereas 6 participants stopped using antidepressants. No further changes were observed in sociodemographic or health characteristics after 40 months of follow-up.

Table 1. Characteristics of 600 patients with a history of MI.

Variables	Baseline n=600	After 40 months of follow-up n=600
Age, mean (SD), years	68.5 (5.5)	71.8 (5.5)
Male, n (%)	488 (81.3%)	488 (81.3%)
Married, n (%)	512 (85.3%)	490 (81.8%)
High education[a], n (%)	95 (15.8%)	95 (15.8%)
Current smoking, n (%)	84 (14.0%)	84 (14.0%)
Alcohol use, n (%)	136 (22.7%)	108 (18.0%)
• No alcohol use	127 (21.4%)	145 (24.7%)
• 1-13 units of alcohol/week	311 (52.4%)	321 (54.6%)
• ≥14 units of alcohol/week	156 (26.3%)	122 (20.7%)
Moderate to poor self-rated health, n (%)	127 (21.2%)	130(21.6%)
Time since last MI, mean (SD), years	3.9 (2.9)	7.3 (2.9)

Participants were included according to completeness of data for all variables.

High education is defined as having more than 11 years of education or having at least completed secondary education.

Table 2. Physical activity and mental well-being variables of 600 patients with a history of MI.

Variables	Baseline	After 40 months
Moderate leisure activities, minutes per day – no. (%)		
• 0 min/day	240 (40.0%)	237 (39.5%)
• 1-29 min/day	147 (24.5%)	139 (23.2%)
• >30 min/day	213 (35.5%)	224 (37.3%)
Moderate and/or vigorous leisure activities, minutes per day – no. (%)		
• 0 min/day	213 (35.5%)	212 (35.3%)
• 1-29 min/day	146 (24.3%)	136 (22.7%)
• >30 min/day	241 (40.2%)	252 (42.0%)
Recommendation for healthy physical activity (n, %)*	241 (40.2%)	252 (42.0%)
MET-minutes per day (median, IQR)**	227 (90-424)	343 (90-476)
Antidepressant use (n, %)	22 (3.7%)	26 (4.3%)
Depressive symptoms (n, %) †	92 (15.3%)	114 (19.0%)
Low optimism (n, %) ‡	93 (15.5%)	79 (13.2%)

Participants were included according to completeness of data for all variables.

* Norm for healthy physical activity is defined as a physical activity lasting more than 30 minutes, during at least 5 days per week, with energy expenditure higher than 3 METs.

**MET: Metabolic Equivalent of Task; GDS-15: 15-item Geriatric Depression Scale; LOT-R: Life Orientation Test Revised.

† Depressive symptoms were defined as having a GDS score$\geq$ 4 points.

‡ Low optimism was defined as having a LOT-R score< 12 points.

Table 2 presents the characteristics at baseline and at 40 months for the main variables physical activity, depressive symptoms, and dispositional optimism. The results show an increase in the percentage of participants reporting moderate and/or vigorous physical activity that fulfilled the recommendation of healthy physical activity, as well as a higher median of MET-minutes per day after 40 months of follow-up. At the same time, there was a slight increase in depressive symptoms and antidepressant use over time. Finally, the percentage of participants that scored low on the optimism scale decreased over time.

Table 3 and Figure 2 present the results of the cross-sectional univariate analyses on the association of physical activity with depressive symptoms and dispositional optimism. There results show a negative cross-sectional association between physical activity and depressive symptoms, both at baseline and after 40 months. Physical activity was cross-sectionally associated with dispositional optimism in the univariate analyses, but this association disappeared after adjustment for covariates (Table 3).

Longitudinal results

Results from the analyses of the associations between absolute changes in physical activity, on the one hand, with absolute changes in depressive symptoms and changes in optimism scores, on the other hand, showed that physical activity changed in synchrony with depressive symptoms (adjusted beta= -0.155; p<0.001) (Table 3). Thus, increases in physical activity were strongly associated with decreases in depressive symptoms over time, and vice versa. By contrast, no reciprocal relationship was found with dispositional optimism, particularly not after adjustment for relevant confounders in Model 2. These results are graphically presented in Figure 2C.

Results from the logistic regression analyses for both depressive symptoms and disposi-

Table 3. Multi-level and longitudinal associations between physical activity, depressive symptoms and dispositional optimism in 600 patients with a history of MI.

Variables	Physical activity			
	Cross-sectional multi-level association		Longitudinal delta association	
	Beta	P-value	Beta	P-value
Depressive symptoms				
• Crude association	−0.225	< 0.001	−0.156	< 0.001
• Model 1	−0.209	< 0.001	−0.154	< 0.001
• Model 2	−0.104	0.02	−0.155	< 0.001
Dispositional optimism				
• Crude association	0.101	0.001	0.042	0.30
• Model 1	0.092	0.002	0.044	0.29
• Model 2	0.052	0.21	0.049	0.24

P-values for linear trend, obtained with linear regression analyses.
Cross-sectional multi-level associations are represented by the beta-coefficients for the cross-sectional association between depressive symptoms and physical activity at baseline and 40 months (taking into account within-subject effects); longitudinal delta associations are represented by the beta-coefficients for the association between the absolute changes (i.e. delta's) over 40 months of depressive symptoms and physical activity.

Model 1: adjusted for age and gender.

Model 2: adjusted for age, sex, education, marital status, smoking habits, alcohol use, treatment group, diabetes mellitus, stroke, time since myocardial infarction, BMI, and MMSE score.

Table 4. Prediction models for baseline physical activity predicting depressive symptoms and dispositional optimism after 40 months of follow-up in patients with a history of MI.

	Baseline moderate and/or vigorous leisure physical activity				
	No activity (ref)	1-29 min/day	p-value	≥ 30 min/day	p-value
Depressive symptoms at 40 months					
• No. of subjects	141	113	–	191	–
• Cases with depressive symptoms at 40 months, n (%)	16 (11.3%)	13 (11.5%)	–	16 (8.4%)	–
• Crude	1.0	1.02 (0.47-2.21)	0.97	0.71 (0.34-1.48)	0.37
• Model 1	1.0	1.01 (0.46-2.20)	0.98	0.76 (0.36-1.58)	0.46
• Model 2	1.0	1.30 (0.53-3.15)	0.57	0.85 (0.38-0.90)	0.58
Low dispositional optimism at 40 months:					
• No. of subjects	166	119	–	208	–
• Cases with low optimism at 40 months, n (%)	18 (10.8%)	10 (8.4%)	–	14 (6.7%)	–
• Crude	1.0	0.75 (0.34–1.70)	0.50	0.59 (0.29–1.23)	0.16
• Model 1	1.0	0.76 (0.34–1.72)	0.51	0.57 (0.27–1.18)	0.13
• Model 2	1.0	0.89 (0.37-2.15)	0.80	0.67 (0.30-1.48)	0.32

Data are presented as OR (95%CI).

* Analyses were done in 445 subjects free of depressive symptoms and antidepressant treatment at baseline. The absence of depressive symptoms was defined as having a GDS-15 score ≤4 points.

** Analyses were done in 493 subjects free of low dispositional optimism scores and antidepressant treatment at baseline. Low dispositional optimism was defined as having a LOT-R score <12 points.

P-values obtained using logistic regression.

Model 1: adjusted for age and gender.

Model 2: adjusted for age, sex, education, marital status, smoking habits, alcohol use, treatment group, diabetes mellitus, stroke, time since myocardial infarction, BMI, and MMSE score.

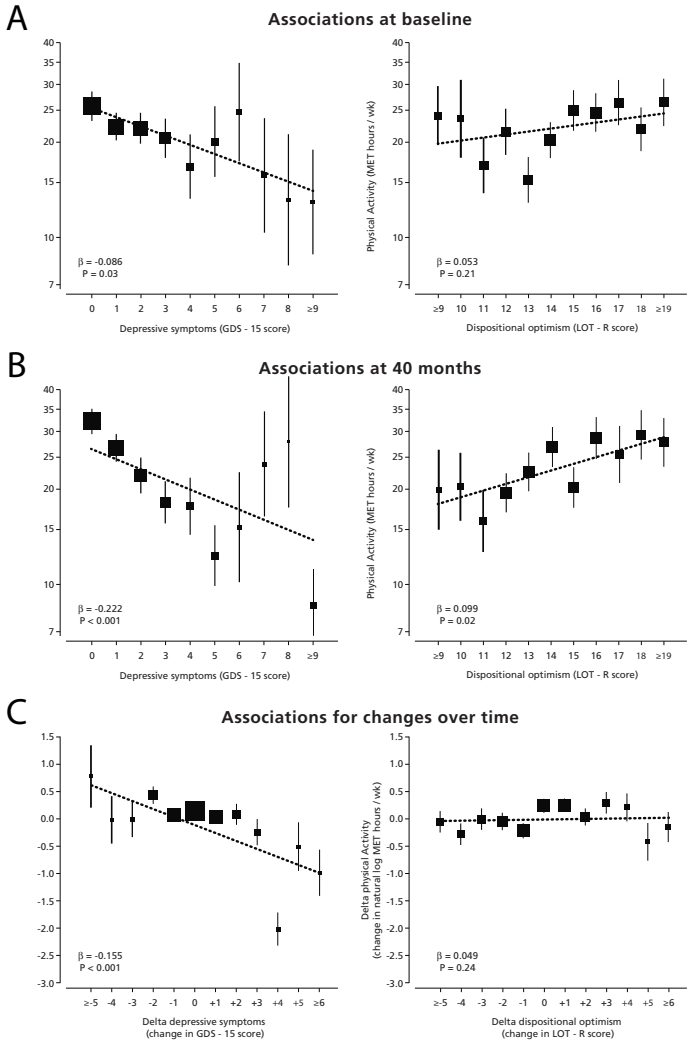


Figure 1. Associations between physical activity on the one hand and depressive symptoms and dispositional optimism scores on the other hand in 600 patients with a history of MI Figure 1A corresponds to the associations at baseline, Figure 1B depicts the association after 10 month of follow-up; Figure 1C shows synchrony of change during follow-up. Mean standard scores (with error bars representing standard errors) are presented. The box size is proportional to the number of patients P-values were obtained with one-way ANOVA analyses for linear trend.

tional optimism are presented in Table 4. Among the participants without depressive symptoms at baseline, participants who reported moderate and/or vigorous activity were not at a statistically significant lower risk of having depressive symptoms after 40 months of follow-up compared to participants who reported no baseline physical activity. Similarly, in those participants without low optimism at baseline, no protective effect of baseline physical activity against low dispositional optimism at 40 months was found.

Discussion

Our study among older subjects with a history of MI showed that physical inactivity was cross-sectionally associated with depressive symptoms, but not with dispositional optimism. We found a reciprocal relationship of physical activity with depressive symptoms, but not with dispositional optimism. Low physical activity at baseline did, however, not predict future depressive symptoms or low dispositional optimism.

A major strength of this study was its prospective longitudinal design and the use of a

validated physical activity questionnaire (i.e. PASE) that allowed retrieving detailed information on common leisure or household activities, which are very relevant in older subjects. Nevertheless, some limitations should be considered. Because physical activity was assessed using a self-report questionnaire, it is possible that the provided information resulted in an overestimation and measurement error of actual physical activities (Conway, Seale, Jacobs, Irwin, & Ainsworth, 2002). Another limitation of our study is that depressive symptoms were assessed using the GDS-15 instead of a structured interview. The GDS-15 is, however, a reliable instrument which specifically assesses depressive symptoms in older subjects with limited items considering somatic symptoms (de Craen et al., 2003), which is particularly relevant in patients with somatic conditions as the symptoms could derive from their somatic condition rather than from depressive symptoms.

Our finding of synchrony of change between physical activity and depressive symptoms is in line with the results of a recent study among older European community-dwelling subjects which found a reciprocal relationship between physical activity and depression (Lindwall, Larsman, & Hagger, 2011). Both studies suggest a dynamic interplay between physical activity and depressive symptoms across time. In our study, however, less physical activity at baseline was not predictive of depressive symptoms at 40 months. The lack of a predictive effect of physical activity on depressive symptoms is in line with several population-based studies among older subjects, which found a cross-sectional, but no longitudinal association between physical activity and depressive symptoms (Weyerer, 1992; Kritz-Silverstein et al., 2001; Cooper-Patrick et al., 1997; Perrino, Mason, Brown, & Szapocznik, 2010). However, our findings are discrepant with some other prospective studies that did find physical activity to predict depressive symptoms in subjects free of depressive symptoms at baseline (Camacho et al., 1991; Farmer et al., 1988; Wise et al., 2006). These inconsistencies could be due to the different questionnaires used to assess physical activity, differences in age, differences in prevalence rates of depressive symptoms, or the inclusion of patients with a history of MI in our study while previous prospective studies were done in the general population.

Our finding of an inverse association between physical activity and depressive symptoms coincides with the results of other cross-sectional studies among patients with cardiovascular disease (Win et al., 2011; Milani et al., 2011). A variety of biological and psychological mechanisms may explain the strong association between these phenomena. Physical activity may positively affect mood by increasing brain levels of monoamines and endorphins (Dishman, 1997; Chaouloff, 1997), or increasing cerebral blood flow (Rogers, Meyer, & Mortel, 1990). Physical activity may also influence depressive symptoms by improving self-esteem and providing a greater sense of self-mastery and autonomy (McAuley et al., 2007; Aamot et al., 2010) . Furthermore, the social interaction that derives from physical activity through sport participation and joining sports clubs may provide social support (Trost, Owen, Bauman, Sallis, & Brown, 2002). Although we cannot exclude the possibility that there is a direct causal relationship between physical activity and depressive symptoms, a likely explanation is that physical activity and depressive symptoms affect each other on the short-term time frame only.

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Chapter 6

Dispositional optimism and loneliness in older men

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Nathaly Rius-Ottenheim
Daan Kromhout
Roos C van der Mast
Frans G Zitman
Johanna M Geleijnse
Erik J Giltay

Abstract

Background Dispositional optimism, defined as a generalized tendency to positive outcome expectancies, is associated with well-being and successful aging. However, it remains unclear whether optimism is also correlated to less feelings of loneliness over time. We aimed to determine whether dispositional optimism is prospectively associated with less feelings of loneliness, independently of potential confounders inherent to the aging process.
Methods We followed 416 older men aged between 70 and 89 years (mean 74.9 years, SD 4.7) within the population-based Zutphen elderly study during up to 10 years of follow-up. Baseline dispositional optimism was assessed using a four-item questionnaire. Presence of feelings of loneliness, the main outcome of our study, was assessed using the 11-item loneliness scale of De Jong Gierveld in 1990, 1993, 1995, and 2000. The association between baseline dispositional optimism and loneliness over time was tested using multilevel regression analysis and adjusting for potential confounders (i.e. age, living arrangement, social contacts, widowhood, memberships, self-rated health, and depressive symptoms).
Results Feelings of loneliness significantly increased during 10 years of follow-up, but showed temporal stability (reliability coefficient 0.78). Low baseline dispositional optimism was strongly associated with loneliness over time, also in the adjusted analysis. A one standard deviation (SD) increase in baseline dispositional optimism was associated with a 0.14 SD (95% confidence interval: 0.04 to 0.23) lower level of loneliness ($F(1, 320) = 7.8$; $p=0.006$).
Conclusions Dispositional optimism is correlated to lower feelings of loneliness over time in older men, independently of depression or changes in social network.

Introduction

Dispositional optimism is a stable personality trait defined as the generalized tendency towards positive outcome expectations, life engagement, and a future orientation (Scheier *et al.*, 1994). Optimists are more likely to engage in problem-solving coping strategies, which enhance their ability to deal with stressful events and consequently improve their psychological well-being (Nes & Segerstrom, 2006). Although the underlying mechanisms are largely unknown, it is conceivable that optimism leads to a more positive appraisal of the existing social network or to the active pursue of new social relationships to cope with adversities (Carver *et al.*, 2010). In this way, dispositional optimism may lead to a better social embedding and protect against loneliness. Although little is known on the potential protective effect of dispositional optimism on loneliness, several cross-sectional studies have shown that optimism is linked to loneliness in low-vision older women (Barron *et al.*, 1992) and college students (Montgomery *et al.*, 2003; Neto & Barros, 2003). However, their cross-sectional designs preclude making causal inferences of the direction of the relationship between optimism and loneliness.

We are only aware of three prospective studies and a cross-lagged longitudinal study investigating the relationship between dispositional optimism, social resources, and loneliness (Brissette *et al.*, 2002; Jackson *et al.*, 2000; Nurmi *et al.*, 1996). The first study investigated the changes and appraisal in social network experienced by a group of 89 students starting college, showing that higher optimism was prospectively associated with greater increases in perceived social support over six months of follow-up (Brissette *et al.*, 2002). The second study examined the effect of dispositional optimism and quality of close relationships on loneliness in 180 students during a six-week follow-up period. They found that lower levels of optimism and social support were associated with more feelings of loneliness (Jackson *et al.*, 2000). The third study investigated the association between cognitive and behavioural strategies and loneliness among 303 students during a one-year follow-up period. Their results indicated that less optimistic students were more likely to use a social-avoidance coping strategy and felt more lonely than their more optimistic peers (Nurmi *et al.*, 1996).

Loneliness is defined as a pervasive state caused by a discrepancy between the individual's desired and actual relationships (Jong-Gierveld, 1987). It has to be discriminated from social isolation, which refers to the more objective absence of social contacts (Routasalo *et al.*, 2006). Weiss (Weiss, 1973) discerned two subtypes of loneliness: emotional and social loneliness. The former is related to the absence of one or more intimate figures, whereas the latter refers to the absence of a broader social network. Emotional loneliness may be particularly relevant when studying older subjects, as they are more likely to suffer bereavement. Furthermore, these losses appear to be more salient for men as they rely more on their spouses and less on other social contacts for seeking support (Antonucci & Akiyama, 1987; Srivastava *et al.*, 2006). There are several known factors underlying loneliness: household composition, social participation, church affiliation, memberships, voluntary work, level of education, income, health, and functional status (Savikko *et al.*, 2005; Wenger *et al.*, 1996). Older adults seem to be at greater risk of feeling lonely due to the inevitable transitions of late life, such as loss of a spouse or disability-related obstacles for social interaction.

The purpose of this prospective study is to investigate the relationship between dispositional optimism and presence of feelings of loneliness in older men. We hypothesize that higher optimism scores at baseline will be associated with less loneliness over time, regardless of (changes in) potential confounders. We base this hypothesis on the findings of previous

research showing that an approach-oriented strategy, which characterizes dispositional optimism, is associated with reduction of loneliness (Masi *et al*., 2010). The elucidation of potential predictors of loneliness is clinically of importance, as the co-occurrence of loneliness with other health problems has been related to a worse prognosis in older adults (Stek *et al*., 2005).

Methods

Study sample

The Zutphen elderly study is a prospective population-based study among older male inhabitants of Zutphen, the Netherlands. The study characteristics of the cohort have previously been described in detail (Feskens *et al*., 1993). Briefly, in 1990, elderly men who were previously examined in 1985 were asked to participate. There were a priori no selection criteria for demographic or health characteristics. Participants were visited for face-to-face interviews and were followed during 10 years. Informed consent was obtained from all study participants. The study was approved by the Medical Ethics Committee of the Leiden University Medical Centre, and in 1995 and 2000, by the Medical Ethics Committee of The Netherlands Organization for Applied Scientific Research (TNO).

Of the 560 subjects who participated in the study in 1990 (response rate 78.0%), 127 subjects were excluded due to missing information on the loneliness or optimism scores, and 17 subjects with a Mini Mental State Examination (MMSE) score <19 were excluded (Folstein *et al*., 1975). Thus, cross-sectional analyses were based on 416 subjects. During the 10 years of follow-up, all surviving cohort members were invited for each consecutive survey wave in 1993 (response rate 70.5%), in 1995 (response rate 74.2%), and in 2000 (response rate 72.8%). During the 10 years of follow-up, 225 subjects (54.1%) of the initial study sample died.

Dispositional optimism

To assess baseline dispositional optimism, participants were tested in 1990 using a four-item questionnaire (Giltay *et al*., 2006a) from a survey of Statistics Netherlands (CBS) consisting of the following statements – "I still expect much from life", "I do not look forward to what lies ahead for me in the years to come", "My days seem to be passing by slowly", and "I am still full of plans" (our translations). Subjects were asked to express the extent of their agreement with each of the items, coding their responses on a 0-2 Likert type scale. Within the four score items, two negatively stated items required reversed coding. The additional answer category "do not know" was also coded as the midpoint (score 1). The optimism questionnaire score ranges from 0-8 points, with higher scores being indicative of higher optimism levels. Internal consistency was of moderate strength (Cronbach's alpha was 0.65 in 1990). The test-retest reliability coefficient was 0.82 for the optimism scale over 10 years.

Loneliness

Feelings of loneliness were assessed in 1990, 1993, 1995, and 2000 using the Loneliness Scale of De Jong Gierveld, an 11-item questionnaire consisting of two subscales: the emotional loneliness scale and the social loneliness scale (Jong-Gierveld, 1987). The loneliness scale comprises five positive stated items and six negative stated items, and ranges from 0-11 points, with higher scores being indicative of higher loneliness levels. The total loneliness score was calculated by assigning a score of one point to the responses indicating a (certain) feeling of loneliness. If a respondent had one missing value, the missing item was imputed

with the median of the remaining 10 items for that particular subject. The emotional loneliness score was the result of the sum of the positively or neutral stated answers on six items, whereas the social loneliness score was the sum of the negatively and neutral stated answers on its five corresponding items. No missing values were allowed for the computation of both subscales. The 11-item De Jong Gierveld Loneliness Scale has proved to be a valid and reliable instrument for the assessment of overall, emotional, and social loneliness (Pinquart & Sorensen, 2001).

Social isolation

Social isolation was assessed in 1990, 1993, 1995, and 2000 using a structured questionnaire on social contacts and memberships. The social contacts questionnaire consists of six items and inquires the frequency of social contacts with relatives and friends (i.e. children living nearby, children living far away, grandchildren, other relatives, friends and acquaintances, and neighbours). The degree of social participation was assessed with a membership questionnaire in which participants reported their degree of participation, if any, in eight organizations of society (i.e. religious community, political organization, social club, sport club, socio-cultural organization, senior club, voluntary work, and other social organizations). A missing value on any of the items of the membership questionnaire was considered as being non-active in that particular organization. Widowhood was dichotomized on being widowed or not, and institutionalized was dichotomized on being institutionalized in a nursing or residential care home, or not.

Possible confounders

Sociodemographic and lifestyle parameters were obtained using structured questionnaires. Educational attainment was categorized into two levels depending on the highest level of education completed; smoking history was classified as no smoking, former smoking, and current smoking. Alcohol consumption was considered high when the consumption was higher than 20 grams of alcohol a day (i.e. two units of alcohol a day). Participants were asked to report their health status (i.e. self-rated health) which was subsequently dichotomized on feeling healthy or feeling (rather) unhealthy (Pijls *et al.*, 1993). Body Mass Index (BMI) was calculated from the measured weight (kg) and height (m). Presence of depressive symptoms was assessed using the Dutch translation of the Zung self-rating depression scale (Zung SDS), with scores >60 indicating presence of depressive symptoms (Zung, 1965; Coulehan *et al.*, 1989). Presence of chronic diseases, defined as having either a cardiovascular disease (i.e. stroke, myocardial infarction, or heart failure), diabetes mellitus, or cancer, was determined by a survey questionnaire and confirmed with hospital discharge data and written information from the general practitioner. Finally, presence of disability was assessed with the 13-item Activities of Daily Living (ADL) questionnaire (van den Brink *et al.*, 2005). Only 13 participants (3.1%) had one missing value on covariates.

Statistical analysis

The baseline characteristics of the participants were compared between not lonely and lonely participants (defined with a cut off score ≥3 on the De Jong Gierveld Loneliness Scale) (Scharf & Jong-Gierveld, 2008), using the chi-square test and two sample t-tests when appropriate. Results are presented as numbers and percentages for categorical variables, and median and interquartile ranges (IQR) for continuous skewed variables. Logistic regression was used to calculate the odds ratios (with 95% confidence intervals [CI]). Reliability coefficients (i.e., an

intraclass correlation coefficient with a one-way random effects model with average-measure reliability) were used to examine temporal stability of loneliness and its two subscales over the four time points.

Linear mixed models were used to assess the progression of the main outcome variable loneliness and its potential confounders over 10 years of follow-up. When statistically significant, post hoc paired comparisons were made by using a Sidak test to identify significant differences for continuous variables and chi-squared tests for categorical variables. Back-transformed geometric means were presented for those continuous variables with a positively skewed distribution which had to be log-transformed before the analysis (i.e. loneliness score and its two subscales, social contacts score, and membership score). Untransformed estimated means were given for those variables with a normal distribution (i.e. dispositional optimism).

Multilevel regression analysis (i.e. linear mixed models) was used to analyse the association of baseline dispositional optimism with loneliness scores from 1993 till 2000 in 316 men. Subjects were measured up to three times and the continuous loneliness score was the main outcome variable. Time was used as a categorical variable with categories corresponding to the years 1990, 1993, 1995, and 2000. In multilevel analysis, we used an unstructured covariance model with a two-level structure consisting of the four observations (lower level) and the subject (higher level). We additionally adjusted for the effects of known confounders (Savikko *et al.*, 2005; Wenger *et al.*, 1996). First, we tested the effect of dispositional optimism on the loneliness scores in a crude model. Subsequently, we adjusted for age, living arrangement, social contacts, widowhood, memberships, self-rated health, and depressive symptoms. Finally, a linear regression analysis was used to explore the correlations between baseline optimism and changes in loneliness scores over time, adjusting for baseline loneliness and the other covariates that were also used in the multilevel regression analysis.

All p-values are two-tailed and considered statistically significant at the level of $p < 0.05$. Data analyses were performed using SPSS for Windows, version 17.0 (Chicago, IL).

Results

Table 1 shows the baseline characteristics of 416 men according to the presence of subjective feelings of loneliness. At baseline, participants were on average 74.8 (S.D. 4.6) years old (range 70 to 89). Loneliness was present in 186 (44.7%) of the participants. It was associated

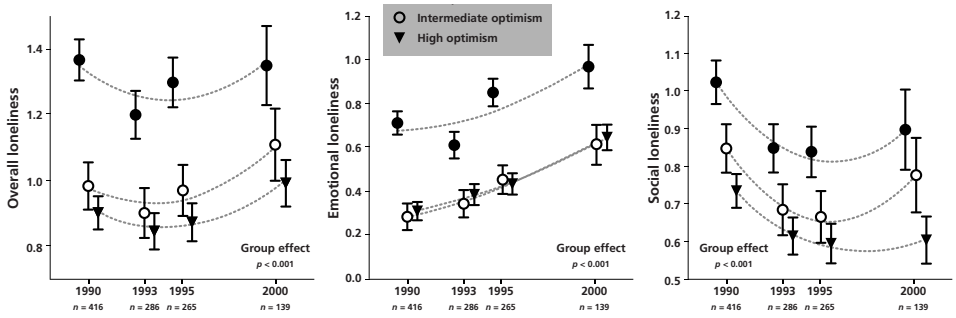

Figure 1. Progression of the total, emotional, and social loneliness scores during 10 years of follow up, according to baseline tertiles of dispositional optimism. Error bars represent 95% confidence intervals of the mean (297 × 210 mm [200 × 200 dots per inch]).

Table 1. Baseline characteristics of 416 elderly men in 1990 according to the loneliness status

	Not lonely	Lonely[a]	OR (95%CI) for loneliness[b]	P-value[c]
N	230	186	–	–
Dispositional optimism, median (IQR)	6.27 (5.00;8.00)	5.16 (4.00;6.00)	0.70 (0.62–0.79)	<0.001
Age, mean ± SD	73.82 (71.00;77.00)	74.86 (71.00;78.00)	1.03 (0.99–1.08)	0.16
Widowhood (n, %)	29 (12.6%)	36 (19.4%)	1.66 (0.98–2.83)	0.06
Living alone (n, %)	31 (13.5%)	49 (26.3%)	2.30 (1.39–3.78)	0.001
Institutionalized (n, %)	8 (3.5%)	4 (2.2%)	0.61 (0.18–2.05)	0.42
Higher education[d] (n, %)	57 (24.8%)	40 (21.6%)	0.84 (0.53–1.33)	0.45
Social contacts, median (IQR)	2.8 (2.6;2.9)	2.6 (2.4;2.9)	0.38 (0.23–0.64)	<0.001
Memberships, median (IQR)	1.4 (0.7;1.8)	1.1 (0.7;1.6)	0.70 (0.53–0.93)	0.01
Smokers (n, %)				
• Never	32 (13.9%)	27 (14.5%)	1.0 (ref)	0.49
• Former	128 (55.7%)	93 (50.0%)	0.86 (0.48–1.53)	
• Current	70 (30.4%)	66 (35.5%)	1.12 (0.61–2.06)	
Alcohol users (n, %)				
• 0 g/ day	50 (21.7%)	48 (25.8%)	1.0 (ref)	0.11
• 1-19 g/ day	121 (52.6%)	106 (57.0%)	0.91 (0.57–1.47)	
• >20 g/ day	59 (25.7%)	32 (17.2%)	0.57 (0.32–1.01)	
Feeling unhealthy (self-rated) (n, %)	100 (43.5%)	105 (56.8%)	1.71 (1.16–2.52)	0.01
Any chronic disease[e], (n, %)	48 (20.9%)	49 (26.3%)	1.41 (0.93–2.12)	0.11
Disability, (n, %)	96 (42.7%)	92 (50.5%)	1.37 (0.93–2.03)	0.11
BMI (kg/m^2), median (IQR)	25.71 (24.02;27.30)	25.27 (22.99;26.91)	0.95 (0.89–1.02)	0.15
Depression, (n, %)	10 (4.5%)	17 (9.4%)	2.21 (0.99–4.95)	0.05
MMSE, median (IQR)	27.00 (25.00;28.00)	27.00 (25.00;28.00)	0.96 (0.88–1.05)	0.36

IQR, interquartile ranges; BMI, body mass index; MMSE, mini mental state examination

a Being lonely was defined as having a loneliness score ≥ 3 points.

b Odds ratios (OR) with 95% confidence intervals (CI) by logistic regression analysis.

c P values by logistic regression analysis.

d Higher education level was defined as having a university or high school degree.

e Chronic disease was defined as having a cardiovascular disease (i.e. myocardial infarction, stroke, and heart failure), cancer or diabetes mellitus.

with low baseline optimism, living alone, and feeling unhealthy, as well as with widowhood and depressive symptoms, but on a borderline statistical significance. Furthermore, loneliness was related to a smaller social network, as evident from the lower social contacts and membership scores.

Table 2 summarizes the progression of the optimism and different loneliness scores from baseline through during follow-up. Optimism scores showed a statistically significant decrease over time. The total loneliness score remained rather stable over time, with an overall reliability coefficient of 0.78 (95% CI: 0.72 to 0.84), when analysing complete data of 128 men at all four time points. The reliability coefficients were 0.76 and 0.79 for the emotional and social loneliness subscales, respectively. As for the loneliness subscales, we observed a statistically significant increase in the emotional loneliness scores and a statistically significant decrease of the social loneliness scores during follow-up. The emotional loneliness scores

Table 2. Time course of dispositional optimism, loneliness and social contacts related factors over 10 years of follow-up in 416 elderly men

	1990 n= 416	1993 n= 286	1995 n= 265	2000 n= 139	P-value
Independent variable:					
• Dispositional optimism score	5.76 (5.58–5.93) [a]	5.31 (5.10–5.51) [b]	5.09 (4.86–5.32) [b]	4.62 (4.36–4.88) [c]	< 0.001
Dependent variables:					
• Loneliness score	1.88 (1.68–2.10)	1.55 (1.35–1.78)	1.72 (1.48–1.97)	1.91 (1.58–2.29)	0.59
• Emotional loneliness subscore	0.50 (0.41–0.59) [a]	0.50 (0.40–0.61) [a]	0.69 (0.56–0.83) [b]	1.00 (0.79–1.23) [c]	< 0.001
• Social loneliness subscore	1.36 (1.21–1.52) [a]	0.98 (0.84–1.13) [b]	0.97 (0.82–1.13) [b]	0.98 (0.79–1.18) [b]	< 0.001
Confounders:					
• Social contacts score	13.43 (12.79–14.07) [a]	5.20 (4.48–6.00) [b]	4.26 (3.64–4.97) [c]	1.37 (1.10–1.67) [d]	< 0.001
• Membership score	2.20 (1.99–2.42) [a]	1.14 (0.99–1.31) [b]	1.08 (0.93–1.24) [b]	0.42 (0.33–0.51) [c]	< 0.001
• Depression (n,%)	27 (6.7%)	27 (6.6%)	23 (8.7%)	10 (7.4%)	0.73
• Widowhood (n,%)	65 (15.6%) [a]	61 (21.3%) [a]	65 (24.4%) [b]	44 (31.0%) [b]	0.001
• Institutionalized (n, %)	12 (2.9%) [a]	12 (4.2%) [a]	9 (3.5%) [a]	19 (13.4%) [b]	< 0.001
• Living alone (n, %)	80 (19.2%) [a]	66 (22.8%) [a]	72 (27.1%)	49 (34.8%) [b]	0.001

Data are backtransformed estimated marginal means (with 95% confidence intervals [CI]), except for dispositional optimism for which untransformed estimated marginal means (with 95% CI) are given.

Data on depression (Zung score>60), widowhood, institutionalized, and living alone are represented as n (%).

Values in the same row with different superscript letters are significantly different (p<0.05) in the post-hoc Sidak test for continuous variables and in the chi-square test for categorical variables.

P-values for linear trend over time using multilevel linear models, except for depression, widowhood, institutionalized, and living alone using chi-squared test linear-by-linear term.

were similar for the years 1990 and 1993, whereupon they increased in 1995 and 2000 (Table 2 and Figure 1). In contrast, social loneliness scores decreased from 1990 until 1993, and remained rather stable thereupon (Table 2 and Figure 1). The cross-sectional Spearman correlation coefficients between emotional loneliness and social loneliness varied in 1990, 1993, 1995, and 2000 between 0.20 and 0.45, showing that emotional and social loneliness scores were positively associated at all time points, but also rather independent constructs. As expected, the percentage of widowers increased during follow-up. Also, the percentage of the participants who were institutionalized in a residential care home and of those who lived alone increased during follow-up. Both social network size and the level of active participation in social organizations showed a strong and highly statistically significant decrease over time.

Table 3 shows both the cross-sectional and longitudinal associations between baseline dispositional optimism and the presence of feelings of loneliness over time. Prospective analyses were based on 316 older men who completed at least one other assessment of loneliness during seven years of follow-up (1993-2000). There was a strong, inverse association between baseline optimism and loneliness scores, with high levels of optimism being related to lower levels of subjective loneliness (effects on the intercept). This association persisted after adjusting for potential confounders. A 1 standard deviation (SD) increase in dispositional optimism was associated with a 0.14-SD lower level of loneliness (95% CI: 0.04 to 0.23; p<0.001). When examining the association between baseline dispositional optimism and the loneliness subscales, we observed a strong inverse association for both emotional loneliness (beta=–0.11; 95% CI: – 0.02 to –0.21; p=0.02), and social loneliness (beta=–0.11; 95% CI: –0.01 to 0.21; p=0.03). Results from the linear regression analysis showed that baseline opti-

Table 3. Prediction of loneliness scores in elderly men according to baseline optimism in 1990 during 7 years of follow-up (1993 till 2000)

	Baseline	Follow-up			
	1990	1993	1995	2000	For 1993 till 2000
Loneliness score					
• Crude	−0.40 (−0.31;−0.48)[a]	−0.26 (−0.14;−0.38)[a]	−0.26 (−0.13;−0.38)[a]	−0.26 (−0.07;−0.44)[b]	−0.27 (−0.17;−0.37)[a]
• Adjusted	−0.30 (−0.21;−0.40)[a]	−0.11 (−0.24; 0.01)	−0.09 (−0.22; 0.03)	−0.18 (−0.38; 0.01)	−0.14 (−0.04;−0.23)[b]
Emotional loneliness score					
• Crude	−0.42 (−0.34;−0.50)[a]	−0.22 (−0.10;−0.34)[a]	−0.29 (−0.16;−0.42)[a]	−0.24 (−0.05;−0.44)[b]	−0.25 (−0.15;−0.35)[a]
• Adjusted	−0.31 (−0.22;−0.39)[a]	−0.11 (−0.23; 0.01)	−0.09 (−0.20; 0.03)	−0.12 (−0.33; 0.04)	−0.11 (−0.02;−0.21)[b]
Social loneliness score					
• Crude	−0.29 (−0.20;−0.38)[a]	−0.16 (−0.03;−0.28)[b]	−0.17 (−0.05;−0.29)[b]	−0.17 (−0.01;−0.34)[b]	−0.18 (−0.09;−0.28)[a]
• Adjusted	−0.24 (−0.13;−0.34)[a]	−0.04 (−0.18; 0.09)	−0.09 (−0.22; 0.02)	−0.12 (−0.29; 0.06)	−0.11 (−0.01;−0.21)[b]

Betas (with 95% confidence intervals) and P-values using multilevel linear models (for 1990 till 2000).

aBetas were significant at p<0.005.

bBetas were significant at p<0.05.

Adjusted for age, living arrangement, social contacts, widowhood, memberships, self-rated health, and depressive symptoms.

mism was not correlated to changes in loneliness scores over time after adjustment for baseline loneliness scores and other covariates (in 1993: beta=−0.01, p=0.82; in 1995: beta=−0.01, p=0.87; in 2000: beta=−0.12, p=0.18).

Figure 1 depicts the impact of time and baseline optimism on the total, emotional, and social loneliness scores. To facilitate presentation of data, categorization of dispositional optimism into tertiles was used instead of continuous data. There was a statistically significant effect of the optimism score on all three loneliness scores (p<0.001), showing that men with the highest optimism scores were not only the least lonely at baseline, but also remained the least lonely throughout the entire follow-up period. Furthermore, we observed a substantial time effect after adjustment for potential confounders, with all three groups of optimism showing an increase of the mean total loneliness and emotional loneliness scores. An attenuated effect of time was observed in opposite direction with regard to the social loneliness scores, which decreased over time. Somewhat contrary to our expectations, the time effect on the decrease in the social loneliness scores could not be explained by the formation of new social contacts in a residential or nursing home, as the time effect persisted after adjustment for social contacts.

Discussion

In this prospective cohort study, lower levels of dispositional optimism at baseline were strongly associated with higher feelings of loneliness in community-dwelling older men. The inverse relationship with baseline dispositional optimism persisted over 10 years of follow-up,

also after adjusting for potential sociodemographic and clinical confounders. Our findings indicate that older men with positive expectations towards the future are less likely to suffer from subjective feelings of loneliness, despite aging-related negative life events such as bereavement and deteriorating health.

There are some limitations that ought to be discussed. Dispositional optimism was assessed with a four-item questionnaire, and not with the more often used LOT-R scale (Life Orientation Test–Revised) (Scheier *et al.*, 1994). However, the four-item questionnaire shares with the LOT-R a focus on the future, having a tendency towards reflecting life engagement, vitality, and having a purpose in life. A further limitation of our study is that our findings cannot be generalized to women, since the Zutphen elderly cohort was only composed of men. Next, it is possible that the advanced age of our sample determined our results. Therefore, it needs to be established whether optimism predicts changes in loneliness in longitudinal studies among younger subjects. The main strength of our study lies on its prospective design with a long follow-up period. In addition, we adjusted for many important confounders, such as social isolation and depressive symptoms, which have been previously reported to be determinants of loneliness. It is well-known that lonely individuals are more susceptible to develop depressive symptoms compared to non-lonely individuals (Luanaigh & Lawlor, 2008; Tijhuis *et al.*, 1999; Prince *et al.*, 1997; Green *et al.*, 1992; Heikkinen & Kauppinen, 2004). Also, low dispositional optimism has been documented as a risk factor for depressive symptoms in older adults (Isaacowitz & Seligman, 2001; Giltay *et al.*, 2006b). It is therefore important to note that the association under study was independent of depressive symptoms. Finally, the internal consistency and reliability of both the optimism and loneliness scales was reasonable, indicating that both optimism and loneliness remained rather stable over time in the old age, despite the gradual within-person decline in optimism with aging.

Our results are consistent with the findings of the aforementioned prospective studies among college students, which reported that lower optimism levels predicted more feelings of loneliness (Jackson *et al.*, 2000; Brissette *et al.*, 2002; Nurmi *et al.*, 1996). We now extend these findings by showing in a prospective study with a longer follow-up period that dispositional optimism was also related to subjective feelings of loneliness in a larger sample of older men. On the other hand, our results contrast with the results of previous studies that found that different precursors and coping strategies were differently associated to emotional or social loneliness in younger adults (Russell *et al.*, 1984; DiTommasso & Spinner, 1993), as we found that low optimism was associated to both emotional and social loneliness scores to a similar extent. The divergence of our results in an old sample with those of the previously described studies among younger samples is probably due to the nature of life-events specific for the elderly. Older adults may be more prone to emotional and social loneliness because of the increasing risk of bereavement due to death of a partner or disability that may hinder activities and social interaction.

The intriguing question remains how dispositional optimism correlates to less feelings of loneliness in older men. Optimism may stimulate ways that people cope with adversity (Andersson, 1996; Fredrickson, 2001) and seek social support (Brissette *et al.*, 2002), enhancing consequently psychological well-being (Isaacowitz & Seligman, 2002). It is conceivable that, after a negative event, optimists use coping strategies that foster more positive appraisals of the existing social network or lead to actively pursue new social relationships (Scheier *et al.*, 1986). In this way, dispositional optimism might lead to the achievement of a better social embedding and protect against feelings of loneliness.

In clinical practice, it has been reported that loneliness is associated with a myriad of

adverse outcomes in the elderly. Loneliness has been related to sleep disturbances (Cacioppo *et al*., 2002; Jacobs *et al*., 2006), poor immune functioning (Glaser *et al*., 1985), poor cardiovascular functioning (Hawkley *et al*., 2006), and increased mortality (Stek *et al*., 2005). Hence, the alleviation of loneliness may improve physical and mental well-being. Our findings suggest that subjects with low levels of optimism are more vulnerable to loneliness and might therefore benefit from more clinical attention and interventions aimed to prevent and alleviate loneliness. In a recent meta-analysis, interventions that addressed maladaptive social cognitions had a superior effect compared to interventions that addressed social support, social skills, and opportunities for social interaction (Masi *et al*., 2010). Their results suggest that maladaptive social cognitions are crucial for the development and maintenance of loneliness, and that reducing social isolation does not necessarily improve feelings of loneliness. In turn, interventions that increase perceived social support may influence self perceptions along dimensions that may improve the quality of social interactions (Cacioppo *et al*., 2006). Future intervention studies should investigate the effects of cognitive and behavioural interventions focused on challenging generalized negative expectations about social relationships, reframing perceptions of loneliness and personal control, and developing more optimistic appraisals that encourage seeking social support as a response to negative cognitions and life events (Hawkley & Cacioppo, 2010; Fava & Tomba, 2009).

We conclude that older men with positive outcome expectations are less likely to experience feelings of loneliness, despite the age-related stressful transitions of late life. Since aging is inevitably related to stressful life events, clinicians and social workers should be aware of the susceptibility of less optimistic older adults to feelings of loneliness in order to offer them adequate care and support.

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Chapter 7

Optimism: identifying a modifiable cognitive marker to promote wellbeing

Submitted for publication

Simon E Blackwell
Nathaly Rius-Ottenheim
Yvonne W. M. Schulte-van Maaren
Victor D. Middelkoop
Frans G Zitman
Philip H. Spinhoven
Emily A. Holmes
Erik J Giltay

Abstract

Optimism is associated with a range of benefits not only for general wellbeing, but also for mental and physical health. The development of psychological interventions to boost optimism derived from emotion research would have the potential to provide significant public health benefits, yet cognitive markers of optimism are little understood. The current study aimed to take a first step in this direction by identifying a cognitive marker for optimism that could provide a modifiable target for innovative interventions. In particular we predicted that the ability to generate vivid positive mental imagery of the future would be associated with dispositional optimism. A community sample of 237 participants completed a survey comprising measures of mental imagery and optimism, and socio-demographic information. Vividness and sense of likelihood of positive future imagery were significantly associated with optimism, even when adjusting for socio-demographic factors and general imagery ability. The ability to generate vivid mental imagery of positive future events may provide a modifiable cognitive marker of optimism. Boosting positive future imagery could provide a cognitive target for treatment innovations to promote optimism, with implications for emotional and even physical wellbeing.

Introduction

Why is it that some people see the future as bright and full of potential, whereas for others it holds only uncertainty or apprehension? Dispositional optimism refers to the tendency to have generalized positive expectancies about the future (Carver, Scheier, & Segerstrom, 2010). Most people show an "optimism bias", expecting positive events rather than negative events to happen in the future, even without supporting evidence (Weinstein, 1980).

It has been argued that optimism is adaptive and an important product of human evolution (Sharot, 2011). An increasing body of evidence suggests that optimism has an impact not only on general wellbeing, but also on mental and physical health (Carver *et al*., 2010). Longitudinal studies have demonstrated that higher levels of optimism are associated with lower cumulative incidence of depression symptoms over a 15-year period (Giltay, Zitman, & Kromhout, 2006), with reduced risk of future cardiovascular disease in a range of populations (Boehm, Peterson, Kivimaki, & Kubzansky, 2011; Giltay, Kamphuis, Kalmijn, Zitman, & Kromhout, 2006; Tindle *et al*., 2009), and even with reduced rate of death (Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004). Optimism is thus linked to positive outcomes in areas that represent huge public burdens of disease such as depression and cardiovascular disease (World Health Organisation, 2004). In the context of the need to develop inexpensive and accessible treatment options (Simon & Ludman, 2009), optimism presents a target for a low-intensity psychological interventions in these areas.

Although some psychological interventions to increase optimism have been described (e.g. Meevissen, Peters, & Alberts, 2011; Riskind, Sarampote, & Mercier, 1996), they have been derived from existing techniques from cognitive behavioural therapy or social psychology. To our knowledge, an empirically-driven treatment based on an understanding of optimism in terms of cognitive and emotional processes is lacking. Developing such an understanding using an "experimental medicine" approach (Rutter & Plomin, 2009) could drive more targeted treatment innovation. This corresponds to the "basic science discovery" phase in the development of new interventions (Thornicroft, Lempp, & Tansella, in press).

A potential neural substrate for optimism has been suggested. Sharot, Riccardi, Raio, and Phelps (2007) found increased activation in the right Anterior Cingulate Cortex (rACC) when participants imagined positive future events, compared to when they imagined negative future events. Furthermore, this relative level of rACC activation was greater for participants with higher levels of self-reported optimism. While the identification of brain regions per se does not easily lend itself to novel treatment development, this study suggests a potentially modifiable cognitive marker: the paradigm used involved the generation of mental imagery, that is, imagining autobiographical episodes.

We propose that a candidate cognitive marker for optimism is the ability to generate vivid mental images of positive events occurring in the future. Imagining the future may play a key role in our day-to-day functioning and has been the subject of much recent research interest (e.g. Addis, Pan, Vu, Laiser, & Schacter, 2009; Crisp, Birtel, & Meleady, 2011; D'Argembeau, Renaud, & Van der Linden, 2011; Schacter, Addis, & Buckner, 2008). Compared to verbal thought, mental imagery has a powerful effect on emotion (Holmes, Coughtrey, & Connor, 2008; Holmes & Mathews, 2005), and thus mental images may be a particularly powerful form of future thinking. What evidence might support our hypothesis? Sharot *et al*. (2007) found that participants reporting higher levels of optimism were more likely to expect the positive events they imagined to happen closer in the future than negative events, and were more likely to experience them with a greater sense of "pre-experiencing".

On the other hand, people with depressed mood showed reduced ability to generate vivid mental images of positive future events (Holmes, Lang, Moulds, & Steele, 2008). Further, Morina, Deeprose, Pusowski, Schmid, and Holmes (in press) found that patients with major depressive disorder and those with anxiety disorders showed reduced ability to generate vivid mental images of positive future events compared to healthy controls, and also rated the events as less likely to occur in the near future. While convergent evidence from both ends of the optimism spectrum suggest that positive future imagery may be important, a key part of the puzzle is missing. That is, in the general population, is optimism associated with greater ability to generate vivid mental images of positive events in the future?

The current study aimed to test the hypothesis that within a large community sample, higher levels of optimism would be associated with the ability to generate more vivid mental imagery of positive future events. We predicted that this relationship would remain significant when adjusting for other potentially confounding variables.

Method

Participants

The study sample was drawn from the Routine Outcome Monitoring (ROM; de Beurs *et al*., 2011) reference study. The ROM reference study comprised a randomly selected population-based sample of Dutch participants aged 18-65, recruited via invitation through their general practitioner. As a reference sample, participants with cognitive difficulties such as dementia, or receiving treatment for a psychiatric disorder within the past 6 months were excluded. The 547 people in the reference study who had agreed to be contacted for research were invited by letter to participate, with the questionnaires and return envelope enclosed, and 258 elected to take part1. Twenty-one participants returned incomplete questionnaires and were excluded, leaving a final sample of 237 (152 men and 85 women).

Measures

Socio-demographic variables (e.g. age, gender, education) were collected as part of the ROM reference study. For the current study, participants further completed the following questionnaires:

Life Orientation Test – Revised (LOT-R; Scheier, Carver, & Bridges, 1994).

This 10-item questionnaire was used to assess dispositional optimism. Items were rated on a 5-point scale from 0 (strongly disagree) to 4 (strongly agree). Three items were positively-worded (e.g. "I'm always optimistic about my future"), three were negatively-worded and reverse-scored (e.g. "I hardly ever expect things to go my way"), and four were filler and not scored. Higher total scores (ranging from 0 through 24) were indicative of higher levels of optimism. The LOT-R has been used in numerous studies investigating optimism (Carver *et al*., 2010), and Scheier *et al*. (1994) report acceptable internal consistency (á = .78), as well as good convergent and discriminant validity.

Prospective Imagery Test (PIT; Holmes, Lang, et al., 2008; Stöber, 2000).

The PIT is a measure of deliberately-generated positive and negative mental images of potential future events. Participants were presented with 10 positive and 10 negative future scenarios and generated a mental image of each. Participants rated the vividness of each image on a scale from 1 (no image at all) to 5 (very vivid). To obtain further information about

the quality of imagery generated (cf. Sharot *et al*., 2007), participants rated their perceived "likelihood" of each event occurring in the near future from 1 (not at all) to 7 (completely), and to what extent they felt that they were "experiencing" each event while imagining it from 1 (not at all) to 7 (completely). In the current study we were primarily interested in responses to the positive items, and included the negative items to control for general ability to generate future imagery. As internal consistency had not previously been reported for subscales of the PIT, we calculated Cronbach's á for our sample. All subscales demonstrated good internal consistency (.83 < á < .90).

Spontaneous Use of Imagery Scale (Reisberg, Pearson, & Kosslyn, 2003).

This 12-item questionnaire was included to control for everyday imagery use. Participants rated items such as ''When I think about visiting a relative, I almost always have a clear mental picture of him or her'' on a scale from 1 (never appropriate) to 5 (always appropriate). Reisberg *et al*. (2003) report excellent internal consistency (á = .98) and good convergent validity.

Results

Table 1 presents descriptive statistics for socio-demographic information2 and measures of imagery (SUIS and PIT), and corresponding zero-order correlations with score on the LOT-R (M = 17.09, SD = 4.37). Vividness, likelihood and experiencing ratings for positive items of the PIT each correlated significantly with score on the LOT-R, suggesting that each of these qualities of the positive future imagery generated was significantly associated with higher levels of optimism.

Hierarchical regression was used to investigate whether the qualities of positive future imagery generated predicted optimism when controlling for other variables. In step 1, socio-demographic variables were entered as control variables. In step 2, the control imagery measures were entered (SUIS, negative PIT subscales). In step 3, the positive subscales of the PIT were entered. Table 1 summarises the regression. Adding the positive subscales of the PIT significantly improved the fit of the model (ÄR2 = .21, ÄF(3, 219) = 24.31, p < .001). In the final model, higher ratings for both vividness and likelihood of positive items on the PIT were significantly associated with higher scores on the LOT-R, and higher experiencing ratings for positive items on the PIT were significantly associated with lower scores on the

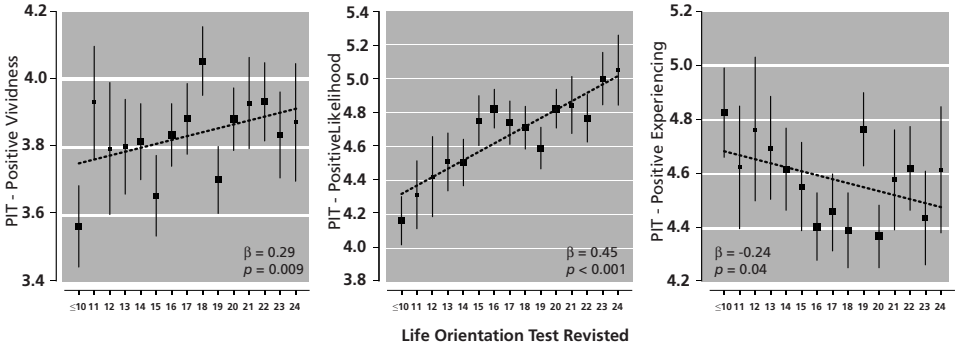

Figure 1. The mean standard scores for the Prospective Imagery Test (PIT) subscales for "vividness", "likelihood" and "experiencing" each event while imagining it in relation to the categorized dispositional optimism score (on the Life orientation test – revised [LOT-R]). The size of each square is proportional to the number of participants. Vertical lines indicate standard errors, and multivariable dashed regression lines are shown. Scores were adjusted as described in Model 3.

Table 1.

Descriptive Statistics and Hierarchical Multiple Regression Analyses Predicting Scores on the Life Orientation Test – Revised via Socio-demographic Data and Measures of Imagery

Predictor	M (SD)	r0	Model 1	Model 2	Model 3
			β	β	β
Age (years)	43.11 (12.61)	.05	.09	.09	.19**
Gender	n (%)				
Female	85 (36%)	.02	-.02	-.005	-.03
Married / Cohabiting	164 (69%)	.22***	.07	.03	.08
Living alone	42 (18%)	-.27***	-.19*	-.19*	-.12
University level education	196 (83%)	.08	.10	.11	.04
Dutch Nationality	231 (98%)	.07	.08	.09	.04
Current smoker	44 (19%)	-.09	-.05	-.04	.001
No or hardly any alcohol use	23 (10%)	-.10	-.05	-.02	.001
Health status					
Self-rated "healthy"	221 (93%)	.20**	0.16*	.13*	.03
Serious illness diagnosed	47 (20%)	.07	0.06	.06	.04
SUIS	35.15 (8.56)	-.03		.009	-.05
PIT-Negative					
Vividness	2.81 (0.97)	-.08		.11	-.09
Likelihood	2.86 (0.97)	-.24***		-.24*	-.19*
Experiencing	2.84 (1.25)	-.15*		-.03	.07
PIT-Positive					
Vividness	3.88 (0.68)	.44***			.29**
Likelihood	4.72 (0.99)	.45***			.45***
Experiencing	4.53 (1.18)	.30***			-.24*
Adjusted R^2			.09	.12	.33
ΔR^2				.04	.21
F for ΔR^2				2.74*	24.31***
Model *F*			3.26**	3.18***	7.74***

Note. N = 237. Model 1 includes socio-demographic variables only. Model 2 additionally includes control imagery variables. Model 3 additionally includes positive future imagery variables. r0 = zero order correlations. SUIS = Spontaneous Use of Imagery Scale. PIT-Negative/Positive = Prospective Imagery Test Positive/Negative items.

*** p < .05. ** p < .01. *** p < .001.**

LOT-R (Figure 1). The only other variables with significant regression coefficients were the likelihood ratings for negative items of the PIT, and age. Examination of residuals plots revealed no multivariate outliers, and no problems with collinearity were identified (inspection of Tolerance/Variance Inflation Factors; Clark-Carter, 2010).

Discussion

This study is the first, to our knowledge, to test the prediction that the ability to generate vivid positive mental imagery of the future is associated with dispositional optimism. Data from a large community sample supported this association. The relationship was significant when controlling for socio-demographic factors and general mental imagery ability. This suggests that further research is warranted in investigating positive future imagery as a potential cognitive marker for optimism and a target for treatment innovation or even prevention in, for example, depression and cardiovascular disease (Giltay *et al*., 2004; Giltay, Zitman, *et al*., 2006).

In addition to imagery vividness, we also considered the characteristics of likelihood and pre-experiencing. The positive future images of more optimistic participants were not only more vivid, but also associated with a sense of greater likelihood of occurring in the near future, and of "pre-experiencing" the imagined event (i.e. the sense of it happening now in the present). This extends the findings of Sharot *et al*. (2007), who found in their fMRI study that more optimistic participants rated imagined positive events as more likely to happen closer in the future than negative events, and experienced these positive events with a greater sense of pre-experiencing. We were able to investigate such relationships within a larger representative sample, and controlling for individual differences in general imagery use.

Additionally, without the constraint of a subtraction condition, as in an fMRI study, we could examine the separate relationships between optimism and the characteristics of positive and negative future imagery on the PIT. We found that the relationship between vividness and optimism was unique to positive imagery. That is, the more vividly someone could imagine a future achievement, for example, the more optimistic they were. For likelihood ratings, both positive and, to a lesser extent, negative imagery independently predicted optimism. That is, optimists showed a greater tendency to endorse, for example, the likelihood of imagined future positive relationships, yet rated imagined future disputes with friends as less likely. Interestingly, once combined in the regression with all other variables, a greater sense of "pre-experiencing" positive events appeared to be associated with lower levels of optimism. This could be interesting to investigate further in future studies as it may be a less useful feature to boost. It could even reflect a psychopathological phenomenon (e.g. in contrast to depression, bipolar disorder is associated with imagery of high "nowness"; Morina *et al*., in press).

Limitations of the study include its correlational nature, which means that issues of causation cannot be explored. Further, fewer than half of those invited to take part in the study elected to take part, and so there could be a self-selecting bias in the study sample. This study represents a critical first step in identifying a modifiable cognitive marker underlying optimism. Current findings suggest that innovative imagery-based interventions to increase optimism should focus on boosting the ability to vividly imagine positive events in the future, e.g. via a computerized, potentially even internet-delivered, intervention (Blackwell & Holmes, 2010), rather than attempting to reduce vividness of negative future imagery (cf. MacLeod & Moore, 2000).

In summary, why is it that some people see the future as bright and full of potential? Current results suggest that when optimists imagine the future they can literally see, in their mind's eye, vivid scenes of positive possibilities. We hope that this research suggests some future developments that will help more people to do the same.

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Chapter 8

General discussion

Introduction

Optimism is traditionally seen as a predictor of better health, but it is possible that mental and physical well-being may influence one's levels of optimism as well. For example, being diagnosed with a severe illness or feeling socially isolated may lower one's level of optimism. Conversely, being in good health, engaging in health promoting behaviors, and perceiving social support probably reinforce one's level of optimism. Furthermore, 'third variables' may mediate and moderate the associations between optimism and health. Until now, most of the scientific work in this field has been devoted to the effects of optimism on physical and mental health status. There has been less focus on whether optimism changes during life and, if so, whether these changes are related to biological, psychological, or lifestyle factors. Also the potential role of third variables in the association between optimism and health has barely been investigated.

The main aim of this thesis was to investigate whether and through what mechanisms dispositional optimism is related to important biological, psychological, and lifestyle correlates. These associations were studied recognizing dispositional optimism as either predictor or outcome of these associations among older people who are especially susceptible to health problems.

Summary of the main findings

In chapter 2 we focused on the question of whether parental longevity is associated with levels of optimism of their offspring. Previous studies had found an association between optimism and longevity within individuals (Chida & Steptoe, 2008; Giltay *et al*., 2004a; Giltay *et al*., 2006; Tindle *et al*., 2009), and family studies had found that parental longevity is related to psychological features of the offspring (Yashin *et al*., 2010). To investigate this association, we used an inter-generational methodological approach in which we examined the relationship between dispositional optimism of the offspring and parental longevity. We conducted our analyses in two independent samples of community-dwelling subjects who had also provided information on their parents' age or age of death. The results of this study showed a consistent inter-generational relationship between parental longevity and dispositional optimism of their offspring. This finding supports the hypothesis that hereditary factors and (very) early environmental factors that predispose some people to high optimism are linked to those that affect longevity. However, these results are preliminary and future studies should explore underlying mechanisms and potential causality in the association between hereditary factors, dispositional optimism, and lifespan.

In chapter 3, we explored the cross-sectional and longitudinal association between a marker of biological aging - telomere length- and dispositional optimism. Previous studies had shown a relationship between telomere shortening and poor mental well-being during adulthood (Simon *et al*., 2006; O'Donovan *et al*., 2009; Panossian *et al*., 2003; Honig *et al*., 2006; Tyrka *et al*., 2009; Epel *et al*., 2004), but whether this association persisted in late life was less well investigated. The results of our study showed no evidence of an association between telomere length and optimism in older adults. These findings contrast with our hypothesis that lower optimism would be associated with shorter telomeres and telomere shortening over time in older adults. However, precisely the old age of our sample may have hampered the detection of an association due to, for example, the higher instability of telomere length at old age. In older people, the enzyme telomerase shortens and elongates

telomeres more arbitrarily, hindering thereby the finding of associations with fluctuations in telomere length (Martin-Ruiz *et al.*, 2005). Future studies investigating telomere length and affective states and traits should therefore take this into consideration.

In chapter 4 we studied C-reactive protein (CRP) as one of the many markers of chronic low-grade inflammation (in absence of infection) in relation to optimism. We analyzed the association between CRP haplotypes and levels of optimism using a Mendelian randomization design that takes adequately into account unobserved confounding and allows the inference of causality (Lawlor *et al.*, 2008; Smith & Ebrahim, 2004; Bochud & Rousson, 2010). Our results showed no overall association between CRP haplotypes and levels of optimism. However, when we stratified for body mass index (BMI) we found that CRP haplotypes that lead to higher CRP plasma levels were also associated with lower levels of optimism in people with obesity (i.e. with a BMI≥ 25 kg/m2). These findings suggest that these CRP haplotypes may be causally related to dispositional optimism, being this association probably modulated by BMI. In other words, low-grade inflammation may adversely affect optimism in obese subjects.

In chapter 5, we examined the association between the lifestyle factor physical activity and optimism in a sample of older subjects with a history of myocardial infarction. As both physical inactivity and low optimism are predictors of less favorable outcomes in patients with cardiovascular disease (Davidson *et al.*, 2010; Giltay *et al.*, 2004b; Woodcock *et al.*, 2010), we hypothesized that they would be strongly interrelated in this population. At baseline, lower optimism levels were only weakly associated with less physical activity. Moreover, no longitudinal association was found on the long-term. These results suggest that physical activity does not beneficially affect levels of optimism over time.

In chapter 6 and 7, we investigated the association between optimism and psychosocial correlates. Chapter 6 described the longitudinal relationship between optimism and loneliness. Given that low optimism and loneliness are both predictors of poor health outcomes, it is possible that optimism is also strongly related to loneliness. Furthermore, loneliness may explain the observed association of low optimism with poor health outcomes. The results of our study among older men showed that higher levels of optimism were predictive of less feelings of loneliness after 10 years of follow-up, even after adjustment for the important covariate depressive symptoms. Our findings suggest that subjects with low levels of optimism are more vulnerable to loneliness and might therefore benefit from more clinical attention and interventions aimed to prevent and alleviate loneliness. Thus, future interventions that enhance optimism may help to reduce feelings of loneliness in older people.

In chapter 7 we reported the results from our study on the cross-sectional association between optimism and mental imagery. Mental imagery, the experience of a visual perception in the absence of external stimuli, is strongly related to emotion and is seen as a possible tool in cognitive behavioral therapy. Earlier studies with a limited follow-up period (i.e. two weeks) have suggested that it is possible to increase optimism through interventions aimed to promote positive visualizations of future events (Peters *et al.*, 2010). Our study showed a strong cross-sectional association between higher levels of optimism and positive mental imagery. These findings, though preliminary, suggest that optimists may have specific properties in their use of mental imagery regarding the future and open new perspectives for cognitive behavioral therapy in making a shift from verbal to visual training exercises in order to increase optimism.

Interpretation of our findings

Effects of biological and lifestyle correlates on optimism

As previously discussed, the benefits of an optimistic outlook on health are manifold. This evidence calls for the identification of factors that may contribute to cultivate optimism and ultimately improve our health status. Recent research suggests that a combination of genetic and environmental influences is involved in one's levels of optimism (Gillham & Reivich, 2004; Vaughan, 2000). Genetic studies among twins have shown that though optimism has a genetic component, our levels of optimism are only determined by genes for only approximately 25% (Plomin *et al.*, 1992). From these results we may deduce that other biological as well as environmental factors have a major impact on our levels of optimism. For example, being a victim of physical or emotional abuse or neglect during childhood leads to lower levels of optimism in adulthood (Gillham & Reivich, 2004). In older adults, biological and lifestyle factors that may influence optimism have been less studied.

Previous studies have shown that optimistic persons live longer (Giltay *et al.*, 2004a; Tindle *et al.*, 2009). Longevity is, in turn, closely related to the length of a cellular marker named telomere (Aviv & Bogden, 2010), the region of repetitive DNA sequences at the end of a chromosome that protects it during replication (Blackburn, 2001). Therefore, we hypothesized that telomere length might help to identify persons with higher or lower optimism levels. The results of this study presented in chapter 4 showed that telomere length is not related to levels of optimism, at least not in the old age. Although this null-finding could also result from the advanced age of our sample or from an attrition bias (Halaschek-Wiener *et al.*, 2008; Martin-Ruiz *et al.*, 2005), it seems unlikely that such a specific cellular marker is directly linked to optimism.

Lifestyle factors, such as physical activity, are traditionally seen as important correlates of an optimistic outlook on life. People who are optimistic are indeed prone to engage in healthy behaviours and are thought to be more physically active (Giltay *et al.*, 2007). Therefore, the question that arose was whether physical activity might increase levels of optimism over time. The results of the study presented in chapter 5 showed that physical inactivity was not predictive of future levels of optimism. So, we may conclude that physical activity per se neither causes fluctuations in optimism on the short-term, nor in the long run.

The results of the studies described in the previous paragraphs show that the influence of biological and lifestyle factors on dispositional optimism were either absent or rather small. Maybe it is not the way they behave what makes optimistic persons maintain their positive outlook on life, but rather the way they think about the future. It has been suggested that the use of mental imagery as a cognitive process encourages more optimistic persons in pursuing their goals, wherein mental imagery refers to the ability of visualizing future events in the mind's eye (Holmes & Mathews, 2010). Generating compelling positive mental images of future events may help to interpret these positive future events as more likely to happen and consequently engage in adaptive behaviours that in the end lead to the achievement of the desired goals (Sharot *et al.*, 2007). The results of the study presented in chapter 8 showed indeed that, in the general population, optimistic persons were able to mentally picture more vivid images of positive events of the future and have a greater sense of likelihood of these events to happen in a near future. Although these findings are correlational, they identify a new cognitive marker that may be of interest in future intervention studies aiming to increase optimism.

Effects of optimism on lifespan and psychosocial correlates

An optimistic outlook on the future has been related to a myriad of positive health outcomes. Optimism has even been shown to predict longevity. In a longitudinal study with a follow-up of 8 years, those participants with a positive outlook on life had a lower risk for all-cause or cardiovascular mortality (Tindle *et al.*, 2009). Also in older adults, optimism was predictive of survival after 15 years of follow-up (Giltay *et al.*, 2004b) . In line with the results of these studies, the findings of the study presented in chapter 2 of this thesis showed an association between longevity and optimism. Because this study had an inter-generational design and showed that parental longevity was associated to optimism of the offspring, our results also provide further support to the hypothesis of shared heritability of optimism and longevity. It is possible that the phenotypes longevity and dispositional optimism have a common heritable component that may be part of a phenotypical spectrum that is inherited together (Martin *et al.*, 2007; Plomin *et al.*, 1992). However, shared heritability is only one of the multiple potential mechanisms that may play a role in this association.

Several studies support the popular notion that optimistic persons are more likely to be married, or to belong to a close family or circle of friends, thereby perceiving more emotional and social support (Brissette *et al.*, 2002; Jackson *et al.*, 2000; Nurmi *et al.*, 1996). The results of the study presented in chapter 7 also show that optimism is predictive of less feelings of loneliness over 10 years of follow-up. These findings are especially relevant in older adults, as it has been shown that loneliness has negative effects on health and decreases survival in older adults (Hawkley & Cacioppo, 2010). Our results support the idea that an optimistic orientation may provide extra benefit to older people as it prevents feelings of loneliness that are so closely related to poor health outcomes.

The role of a third variable in the association between optimism and health

There are many complex mechanisms that may underlie the association between optimism and health outcomes. It is possible that the association between optimism and good health is mediated or moderated by third variables. We have studied some of these numerous possibilities. We found no support for such a relationship with physical activity. In our study among subjects with a history of myocardial infarction, higher levels of physical activity were not predictive of higher levels of optimism over time. Thus, physical activity is unlikely to enhance optimism and does not mediate the previously found association between optimism and longevity. Other more specific biological characteristics, such as the rate of telomere shortening, do neither affect levels of optimism. Thus, higher levels of optimism seem to be independent of cellular longevity. This conclusion suggests that the observed association between optimism and longevity is not reflected at the cellular level of telomere lengths.

Obesity, by contrast, seemed to play a moderating role in the association between optimism and levels of the inflammatory marker CRP. In our study, we found that optimism was associated with the inflammatory marker CRP, but only in obese or overweight subjects. These finding of lower levels of optimism in obese subjects prone to high CRP levels may explain part of the higher cardiovascular mortality rates found among these persons. From the results presented in chapter 4, we may conclude that obesity is a moderator of the association between optimism and inflammation.

There are many other potential "third variables" that may moderate or underlie the association between optimism and longevity that have not been considered in this thesis. These

potential third factors may have a behavioral or physiological nature. More adaptive coping has been posited as one behavioral mechanism explaining the association of optimism with lower mortality risk. As optimists consider being healthy a desirable goal, they engage in health-promoting lifestyles, such as non-smoking, increased physical activity, moderate alcohol use and consumption of more fruits, vegetables, and whole grains (Giltay *et al*., 2007; Steptoe *et al*., 2006; Kelloniemi *et al*., 2005) and adhere better to medical treatment (DiMatteo *et al*., 2000). Furthermore, it is also possible that the association between optimism and longevity is mediated by physiological mechanisms. Dispositional optimism may influence health through the regulation of the autonomic nervous system by attenuating the sympathetic nervous system activity and enhancing parasympathetic activity, as evident from the increased heart rate variability and lower blood pressure observed in optimists (Steptoe, 2007). These effects may also derive from the reduced hypothalamic-pituitary-adrenal axis (HPA axis) reactivity to stressors observed in persons with high optimism (Chida & Hamer, 2008). Another possible underlying mechanism that may explain the association between optimism and longevity is the regulation of immune processes. Several studies have shown that optimism may buffer the negative impact of stress on immune responses. For example, during situations of acute tress that are often accompanied by reduced lymphocyte turnover, optimistic persons display increased numbers of cytotoxic T cells, improved natural killer cell (NKC) activity, and larger antigen-stimulated delayed-type hypersensitivity responses (Segerstrom, 2001; Segerstrom & Sephton, 2010). However, the relationship between optimism and immunity is highly complex and dependent on the duration and nature of the stressor or pathogen involved (Cohen *et al*., 1999). Moreover, little is known about the potential effect of optimism on the interaction between the HPA axis, the autonomic nervous system, and immune responses.

Table 1. Characteristics of cohorts used in the studies presented in this thesis

	Arnhem Elderly Study	Alpha Omega Study	Cretan Elderly Study	Leiden Longevity Study	ROM reference group	Zutphen Elderly Study
Number of participants	426	769*	123	1252	242	416*
Age (years); mean ± SD	74.3 ± 5.7	69.2 ± 5.7	84.1 ± 4.2	66.1 ± 6.4	43.0 ± 12.7	74.8 ± 4.6
Male sex (%)	48%	77%	100%	48%	64%	100%
Comorbidity	Population-based sample	Post-MI patients	Population-based sample	Population-based sample	Population-based sample	Population-based sample
Optimism instument	SSWO	LOT-R	4Q	LOT-R	LOT-R	4Q
Chapters in this thesis	4	2,5	3	2,4	7	3, 4, 6

SSWO: Scale of Subjective Well-being of Older People; LOT-R: Life Orientation Test-Revisted; MI: myocardial infarction; ROM: Routine Outcome Monitoring; 4Q: 4-item optimism questionaire.

*** Given the different exclusion criteria used across the studies presented in this thesis, this table presents only the highest sample size used.**

Methodological considerations

Albeit the use of different instruments used to assess optimism, we found consistent results across different samples of older people (see Table 1). To ensure comparability, we homogenized all variables across samples and we included only participants without missing values for the main variables and covariates. Nevertheless, we also would like to highlight the following issues which may limit the interpretation of our results. First, the focus on older populations may have resulted in an attrition bias due to selective survival of the healthiest subjects. Second, some of the samples were only composed of men; which hampers the generalization of our results to women. Third, the use of self-report (though well validated) questionnaires for variables such as physical activity in these older people may have resulted in an underestimation of the effects due to a recall bias. Finally, most of our studies were of observational nature, restricting the identification of confounders and the inference of causality.

Implications for general and clinical practice

Optimism is related to positive health outcomes, commitment to self-care, social functioning, and a better adherence to medical treatment (Carver *et al*., 2010; DiMatteo *et al*., 2002). Although it is insufficiently clear whether the relationship between optimism and good health is causal, the importance of identifying persons at risk for poorer prognosis can hardly be overemphasized in clinical practice. The assessment of optimism may help to recognize older people at risk for somatic and psychological health problems. From the studies presented in this thesis, it seems that low levels of optimism are associated with a shorter lifespan, a higher risk of inflammation in obese persons, and more feelings of loneliness. Moreover, our work supports a strong relationship between optimism and positive mental imagery. As these results are correlational, future intervention studies could investigate whether levels of optimism are modifiable on the long term by means of a cognitive therapy based on mental imagery. If so, people with lower levels of optimism could be offered interventions to strengthen personal resilience and enhancing optimistic dispositions that might help them to recover from setbacks or diseases. Furthermore, mobilizing their social resources may be helpful to avoid problems related to loneliness.

Future directions of research

Lately, interest is shifting beyond stress, disease and psychopathologic factors towards the exploration of resilience and other factors that promote health and thriving. Optimism is one of these factors that are related to a greater resilience and help people to cope with adversities. Moreover, optimism is easily assessed with self-report questionnaires that can be included in large epidemiological studies. It is also necessary to collect optimism data at frequent intervals over lengthy follow-up periods to address questions about its fluctuations across lifespan and its link to health outcomes in more detail. In this way, the cumulative exposure, possible fluctuations, and outcome of optimism may be studied in relation to disease and health states.

In future studies, the overlap of optimism with other constructs, such as positive affect, low neuroticism, or extraversion, should also be addressed. Studies have often used these psychological concepts as synonyms of optimism, but they are not equivalent. Future studies should therefore differentiate optimism from these overlapping psychological con-

structs. Furthermore, to demonstrate a causal relationship between optimism and health, randomized trials investigating whether a (psychotherapeutic) intervention aimed at boosting optimism in patients can make a meaningful difference in long-term health are needed. In our work we found preliminary evidence for an association between optimism and positive mental imagery, which is the ability to visualize positive future events. Mental imagery has been successfully used in cognitive behavioral therapy and it is possible that including positive mental visualizations of the future may increase levels of optimism. However, it is yet to be investigated whether changes in optimism achieved through mental imagery interventions are endurable.

Conclusion

Throughout the studies presented in this thesis, our findings fit the hypothesis that optimism predicts enhanced mental well-being and longevity, but also that levels of optimism within a certain person are rather stable over time and resistant to change. However, this stability of optimism does not necessarily imply that no fluctuations in optimism are possible. Certain positive or negative life events are likely to provoke small changes in optimism. But it is possible that dispositional optimism is a stable personality trait that cannot be learned or wherein only little changes are possible. Thus, as things stand, it remains unclear whether adopting a more positive outlook on life can enhance your likelihood of survival. Thoughtfully designed future clinical and epidemiologic studies are required to explore the potential benefits of boosting optimism. But it certainly would not hurt – and it might put a smile on your face– to see the glass half full.

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Chapter 9

Summary

1. English summary

Dispositional optimism refers to the extent to which people have positive generalized expectancies towards future events. Highly optimistic persons expect good things rather than bad things to happen in their future. This conviction of attainability of desired outcomes results in goal-oriented coping strategies that enhance the perception of controllability of stressors. Thus, optimists face adversities using a proactive adaptive approach to deal with the source of stress, whether it concerns a health, psychological or a social problem.

The benefits of an optimistic outlook on life are manifold. Previous studies have shown that higher levels of optimism are associated with better subjective health measures such as perceived health or a better functional status, as well as objective health measures, such as slower disease progression or reduced mortality. Optimism has also been associated with better psychological well-being, less depressive symptoms, and better psychological adjustment to chronic diseases.

Previous research suggests that a person's level of optimism stems from a combination of genetic and environmental influences. However, the genetic component of dispositional optimism only explains 25% of the inter-individual variability in levels of optimism. Therefore, it is likely that other biological or environmental factors have a major impact on our levels of optimism. This evidence calls for the identification of factors that may contribute to cultivate optimism and ultimately improve our health status. Several studies have shown that optimism is inversely associated with age, and especially during aging optimism seems to decline in the few prospective studies that have been conducted. This poses the interesting question as to which factors reduce the risk of a decline in optimism. However, until now, very limited data have been available on factors that may influence optimism at old age.

The main aim of this thesis was to investigate whether and through which mechanisms dispositional optimism relates to important biological, psychological, and behavioral aspects in old age. Therefore, these associations were studied exploring dispositional optimism as either predictor or outcome of these associations.

To place our studies in context, we started by conducting a review on the existing studies in the field of optimism (Chapter 1). From the literature reviewed in this first chapter, we conclude that dispositional optimism is strongly correlated with better physical and mental well-being. Specifically, a strong association had been found between low levels of optimism and cardiovascular disease. Yet, the mechanisms through which optimism relates to better health outcomes remained to be elucidated.

The study described in chapter 2 focused on the question of whether parental longevity was associated with levels of optimism of the offspring. Previous studies found an association between optimism and longevity within individuals, whereas family studies had found that parental longevity is related to psychological features of the offspring. To investigate this association, we used an inter-generational methodological approach in which we examined dispositional optimism of the offspring in relation to parental longevity. The results of this study showed a consistent inter-generational relationship between parental longevity and dispositional optimism of the offspring. This finding supports the hypothesis that hereditary factors and (very) early environmental factors that predispose some people to high optimism are linked to those that affect longevity.

In chapter 3, we explored the cross-sectional and longitudinal association between a marker of biological aging - telomere length- and dispositional optimism. Previous studies had shown a relationship between telomere shortening and poor mental well-being during

adulthood, but whether this association persisted in late life was less well investigated. The results of our study showed no evidence of an association between telomere length and optimism in older adults. These findings contrast with our hypothesis that lower optimism would be associated with shorter telomeres and telomere shortening over time in older adults. However, precisely the old age of our sample may have hampered the detection of an association due to, for example, the higher instability of telomere length in old age. In older people, the enzyme telomerase shortens and elongates telomeres more arbitrarily, hindering thereby the finding of associations with fluctuations in telomere length. Future studies investigating telomere length and optimism should therefore take this consideration into account.

Chapter 4 describes the study on C-reactive protein (CRP), one of the many markers of chronic low-grade inflammation (in absence of infection), in relation to optimism. While most previous studies did not study causality, we analyzed the relationship between CRP haplotypes and levels of optimism using the so-called Mendelian randomization design. This method allows the inference of causality adequately taking into account unobserved confounding of third variables. Our results showed no overall association between CRP haplotypes and levels of optimism. However, when we stratified for body mass index (BMI) we found that CRP haplotypes that lead to higher CRP plasma levels were also associated with lower levels of optimism in people with overweight or obesity (i.e. with a BMI> 25 kg/m2). These findings suggest that CRP haplotypes that relate to higher plasma CRP levels may be causally related to dispositional optimism and that this association is probably modulated by BMI. In other words, low-grade inflammation may adversely affect optimism in obese subjects.

In chapter 5 we examined the association between the lifestyle factor physical activity and optimism in a sample of older subjects with a history of myocardial infarction. As both physical inactivity and low optimism are predictors of less favorable outcomes in patients with cardiovascular disease, we hypothesized that they would be strongly interrelated in this population. At baseline, lower optimism levels were only weakly associated with less physical activity. Moreover, no longitudinal association was found on the long-term. These results suggest that physical activity does not beneficially affect levels of optimism over time. By contrast, we found a solid association between physical activity and depression.

In chapter 6 and 7 we investigated the association between optimism and psychosocial factors. Chapter 6 described the longitudinal relationship between optimism and loneliness. Given that low optimism and loneliness are both predictors of poor health outcomes, it is possible that optimism also predicts less loneliness. Furthermore, loneliness may explain the observed association of low optimism with poor health outcomes. The results of our study among older men showed that higher levels of optimism were predictive of less feelings of loneliness during 10 years of follow-up, even after adjustment for the important covariate depressive symptoms. Our findings suggest that subjects with low levels of optimism are more vulnerable to loneliness and might therefore benefit from more clinical attention and interventions aimed to prevent and alleviate loneliness. Thus, future interventions that enhance optimism may help to reduce feelings of loneliness in older people.

In chapter 7 we report the results from our study on the cross-sectional association between optimism and mental imagery. Mental imagery, the experience of a visual perception in the absence of external stimuli, is strongly related to emotion and is seen as a possible tool in cognitive behavioral therapy. Earlier studies with a limited follow-up period (i.e. two weeks) have suggested that it is possible to increase optimism through interventions aimed to promote positive visualizations of future events. Our study showed a strong cross-sectional

association between higher levels of optimism and positive mental imagery. These findings, though preliminary, suggest that optimists may have specific properties in their use of mental imagery regarding the future and open new perspectives for cognitive behavioral therapy in making a shift from verbal to visual training exercises in order to increase optimism.

Conclusion

The findings presented in this thesis fit the hypothesis that optimism is associated with enhanced mental well-being and longevity, but also that levels of optimism within a certain person are rather stable over time and resistant to change. However, this stability of optimism does not necessarily imply that no fluctuations in optimism are possible. Certain positive or negative life events are likely to provoke small (but temporary) changes in optimism. But it is possible that dispositional optimism can hardly be learned and that only little changes are possible in an otherwise relatively stable personality trait. Thoughtfully designed future clinical and epidemiologic studies are required to explore the potential benefits of optimism. But it certainly would not hurt – and it might put a smile on your face– to see the glass half full.

2. Nederlandse samenvatting

Dispositioneel optimisme verwijst naar de mate waarin mensen algemene positieve verwachtingen hebben jegens toekomstige gebeurtenissen. Zeer optimistische mensen zien hun toekomst rooskleuriger in dan minder optimistische mensen. De overtuiging dat gewenste resultaten haalbaar zijn, leidt tot doelgerichte strategieën, wat weer de perceptie van beheersbaarheid van stressoren kan verbeteren. Optimisten lijken met hun pro-actieve, adaptieve benadering bronnen van stress beter aan te pakken, of het nu een gezondheids-, psychologisch of maatschappelijk probleem betreft.

Er zijn talrijke voordelen van een optimistische kijk op het leven. Eerdere studies hebben aangetoond dat meer optimisme gerelateerd is aan een betere subjectieve gezondheid, zoals ervaren gezondheid of een betere functionele status; maar ook aan objectieve gezondheidsmaten, zoals een tragere progressie van een chronische ziekte of een lagere mortaliteit. Optimisme is ook in verband gebracht met een beter psychisch welbevinden, minder depressieve symptomen en betere psychologische aanpassing aan chronische ziekten.

Eerder onderzoek suggereert dat een combinatie van genetische en omgevingsfactoren bepaalt hoe optimistisch iemand is. De genetische bijdrage van optimisme verklaart echter slechts 25% van de inter-individuele variabiliteit in de mate van optimisme. Het is dus waarschijnlijk dat andere biologische of omgevingsfactoren een belangrijke invloed hebben op het niveau van optimisme. Daarom is het belangrijk die factoren te identificeren die kunnen bijdragen aan het verhogen van optimisme en daardoor onze gezondheid kunnen verbeteren. Verschillende studies hebben aangetoond dat optimisme invers geassocieerd is met leeftijd; optimisme neemt af met oudere leeftijd in de weinige prospectieve studies die zijn uitgevoerd. Dit roept de interessante vraag op van welke factoren het risico vormen voor een afname van optimisme. Er zijn tot nu toe slechts beperkte gegevens beschikbaar over factoren die van invloed kunnen zijn op optimisme op oudere leeftijd.

Het hoofddoel van dit proefschrift is te onderzoeken of, en via welke mechanismen, optimisme geassocieerd is met belangrijke biologische, psychologische en gedragsmatige aspecten op oudere leeftijd. Daarom wordt optimisme zowel als voorspeller als als uitkomst van deze associaties onderzocht.

Om het eigen onderzoek in een context te plaatsen is eerst literatuuronderzoek verricht naar bestaande studies op het gebied van optimisme (hoofdstuk 1). Hieruit blijkt dat optimisme sterk geassocieerd is met een beter lichamelijk en psychisch welzijn. Vooral het verband tussen hart- en vaatziekten en een lage mate van optimisme is sterk. Echter, de mechanismen waarmee optimisme betrekking heeft op een betere gezondheid moeten nog worden opgehelderd.

Het onderzoek beschreven in hoofdstuk 2 richt zich op de vraag of langlevendheid van de ouders geassocieerd is met de mate van optimisme van hun kinderen. Eerdere studies hebben een verband gevonden tussen optimisme en levensduur in individuen, hetgeen later in familiestudies werd bevestigd door de bevinding dat langlevendheid van de ouders gerelateerd is aan psychologische kenmerken van hun kinderen. Om deze associatie te onderzoeken, gebruiken we een intergenerationele methodologische aanpak, waarbij optimisme van de nakomelingen onderzocht is in relatie tot langlevendheid van de ouders. Een consistente associatie werd gevonden tussen een langere levensduur van de ouders en optimisme van hun kinderen. Deze bevinding ondersteunt de hypothese dat erfelijke factoren en (zeer) vroege omgevingsfactoren van invloed kunnen zijn op de mate van optimisme en dat deze factoren ook gekoppeld kunnen zijn aan de factoren die langlevendheid beïnvloeden.

In hoofdstuk 3 wordt de cross-sectionele en longitudinale associatie tussen een 'marker' van biologische veroudering - de lengte van telomeren- en dispositioneel optimisme onderzocht. Eerdere studies hebben een relatie aangetoond tussen telomeerverkorting en een slechter psychisch welzijn in de volwassenheid; maar of deze associatie ook aanwezig is op oudere leeftijd is minder goed onderzocht. De resultaten van onze studie tonen geen bewijs van een verband tussen de lengte van telomeren en het niveau van optimisme bij oudere volwassenen. Deze bevindingen zijn in tegenspraak met onze hypothese dat lager optimisme geassocieerd is met kortere telomeren en telomeerverkorting bij oudere volwassenen. Juist de ouderdom van onze steekproef kan het opsporen van een duidelijke associatie echter hebben bemoeilijkt, aangezien op hogere leeftijd de telomeerlengte meer instabiel is. Het enzym telomerase zorgt ervoor dat verkorte telomeren weer verlengd worden, hetgeen op oudere leeftijd op een meer willekeurige manier gebeurt. Dit bemoeilijkt het vinden van een associatie tussen optimisme en telomeerlengte. Toekomstige onderzoeken naar een associatie tussen telomeerlengte en optimisme zouden hier rekening mee moeten houden.

In hoofdstuk 4 is het C-reactief proteïne (CRP) als een van de vele markers van chronische ontsteking (in afwezigheid van infectie) in relatie tot optimisme bestudeerd. Aangezien de meeste eerdere studies geen causaliteit tussen beide hebben aangetoond, analyseren we in deze studie de associatie tussen CRP haplotypes en de mate van optimisme door gebruik te maken van de Mendeliaanse randomisatiemethode. Door middel van deze methode wordt adequaat rekening gehouden met de onbekende, verstorende effecten van andere variabelen die het oorzakelijk verband kunnen maskeren. Onze resultaten tonen geen algemeen verband aan tussen CRP haplotypes en de mate van optimisme. Na stratificatie voor de body mass index (BMI) vinden we echter dat de CRP haplotypes die geassocieerd zijn met hogere CRP plasmaspiegels ook geassocieerd zijn met een lager niveau van optimisme bij mensen met obesitas (BMI> 25 kg/m2). Deze bevindingen suggereren dat ontsteking genotypisch is geassocieerd met optimisme en dat dit verband gemoduleerd wordt door BMI. Met andere woorden, chronische ontsteking met hogere CRP spiegels heeft een negatieve invloed op het niveau van optimisme bij mensen met overgewicht.

Hoofdstuk 5 beschrijft het mogelijke verband tussen de levensstijl factor lichamelijke activiteit en optimisme in een steekproef van oudere patiënten met een myocardinfarct in hun voorgeschiedenis. Aangezien zowel lichamelijke inactiviteit als een laag optimisme voorspellers zijn van minder gunstige uitkomsten bij patiënten met hart-en vaatziekten, formuleren we de hypothese dat beide factoren in deze populatie sterk geassocieerd zouden zijn. Cross-sectioneel zijn lagere niveaus van optimisme slechts zwak geassocieerd met minder lichamelijke activiteit. Bovendien werd op de lange termijn geen longitudinaal verband gevonden. Deze resultaten suggereren dat lichamelijke activiteit het niveau van optimisme op langere termijn waarschijnlijk niet kan beïnvloeden. Depressie is daarentegen wel geassocieerd met verminderde lichamelijke activiteit.

De hoofdstukken 6 en 7 beschrijven het verband tussen optimisme en psychosociale factoren. Hoofdstuk 6 schetst de longitudinale relatie tussen optimisme en eenzaamheid. Gezien laag optimisme en eenzaamheid beide voorspellers zijn van een slechtere gezondheid, is het mogelijk dat optimisme ook gerelateerd is aan eenzaamheid. Bovendien zou eenzaamheid de waargenomen associatie tussen laag optimisme en slechte gezondheid kunnen verklaren. De resultaten van ons onderzoek onder oudere mannen tonen aan dat een hogere mate van optimisme voorspellend is voor minder gevoelens van eenzaamheid gedurende een 10 jaar durende follow-up; zelfs na correctie voor de belangrijke verstorende variabele depressieve symptomen. Onze bevindingen suggereren dat patiënten met laag optimisme kwetsbaarder

zijn voor eenzaamheid en daardoor mogelijk kunnen profiteren van meer klinische aandacht en interventies gericht op het voorkomen en verlichten van eenzaamheid. Zo zouden toekomstige interventies welke optimisme versterken, ook kunnen helpen om gevoelens van eenzaamheid te verminderen bij oudere mensen.

Hoofdstuk 7 omschrijft de resultaten van onze studie naar het cross-sectionele verband tussen optimisme en mentale beeldvorming. Mentale beeldvorming, de ervaring van een visuele waarneming bij de afwezigheid van externe prikkels, is sterk gerelateerd aan emoties en wordt gezien als een mogelijk hulpmiddel in cognitieve gedragstherapie. Eerdere studies met een beperkte follow-up periode (twee weken) suggereerden de mogelijkheid optimisme te verhogen door middel van interventies bedoeld om positieve visualisaties van toekomstige gebeurtenissen te bevorderen. Onze studie toont een sterk cross-sectioneel verband tussen een hogere mate van optimisme en positieve mentale beeldvorming. Deze voorlopige bevindingen suggereren dat optimisten specifieke eigenschappen hebben in hun gebruik van mentale beeldvorming ten aanzien van de toekomst en openen nieuwe perspectieven voor het gebruik van cognitieve gedragstherapie. Door het toepassen van zogeheten mentale beeldvormingstechnieken kan optimisme mogelijk versterkt worden.

Conclusie

De bevindingen beschreven in dit proefschrift bevestigen onze hypothese: optimisme is geassocieerd met een beter psychisch welbevinden en langlevendheid. Echter suggereren onze bevindingen ook dat de mate van optimisme binnen een bepaald persoon vrij stabiel is in de tijd en nauwelijks verandert. Deze stabiliteit van optimisme betekent niet dat er geen schommelingen in optimisme mogelijk zijn. Bepaalde positieve of negatieve levensgebeurtenissen kunnen duidelijke (maar tijdelijke) veranderingen in optimisme teweeg brengen. Het is echter mogelijk dat optimisme niet kan worden geleerd en slechts kleine veranderingen kunnen optreden in deze relatief stabiele persoonlijkheidskenmerk. Toekomstige klinische en epidemiologische studies zijn nodig om de potentiële voordelen van optimisme verder te kunnen leren begrijpen. Maar het zou zeker geen kwaad doen om het glas half vol te zien.

3. Resumen de la tesis.

El optimismo disposicional hace referencia a la medida en que la gente tiene expectativas positivas generalizadas sobre acontecimientos futuros. Las personas muy optimistas tienen la expectativa de que les van a suceder cosas buenas en lugar de cosas malas en un futuro. Precisamente es esta convicción de que van a alcanzar los objetivos deseados lo que les lleva a utilizar estrategias dirigidas a conseguirlo, y hace que tengan la percepción de que pueden controlar la fuente de estrés. De este modo, las personas optimistas hacen frente a las adversidades con un enfoque proactivo, ya se trate de problemas de salud, psicológicos o problemas de índole social.

Los beneficios de una visión vital optimista son múltiples. Estudios anteriores han demostrado que altos niveles de optimismo están asociados con medidas de salud subjetiva, tales como la percepción de salud positiva o un mejor estado funcional, y medidas objetivas, como una progresión más lenta de enfermedades crónicas o una reducción de la mortalidad. El optimismo también se ha asociado con un mayor bienestar psicológico, menos síntomas depresivos, y un mejor ajuste psicológico a enfermedades crónicas.

Investigaciones previas sugieren que los niveles de optimismo derivan de una combinación de influencias genéticas y ambientales. Sin embargo, el componente genético del optimismo disposicional tan sólo explica el 25% de la variabilidad interindividual en los niveles de optimismo. Por lo tanto, es probable que otros factores biológicos o ambientales tengan también un gran impacto en nuestros niveles de optimismo. Estos datos llaman a la identificación de factores que puedan contribuir a fomentar el optimismo y, en definitiva, mejorar nuestro estado de salud. Estudios previos han mostrado una asociación inversa del optimismo con la edad, en concreto, según los estudios prospectivos realizados hasta el momento, los niveles de optimismo parecen disminuir a edades más avanzadas. Sin embargo, hasta ahora, hay muy pocos datos disponibles sobre los factores que pueden influir en el optimismo a estas edades.

El objetivo principal de esta tesis ha sido investigar si el optimismo disposicional está relacionado con importantes aspectos biológicos, psicológicos y conductuales en edades avanzadas y a través de qué mecanismos. Con este propósito se estudiaron estas asociaciones explorando el rol del optimismo disposicional ya fuera como determinante o como resultado de las mismas.

Para colocar nuestros estudios en contexto llevamos a cabo una revisión de los estudios existentes en el campo del optimismo (Capítulo 1). De la literatura revisada en este primer capítulo se puede concluir que el optimismo disposicional está fuertemente relacionado con mejor bienestar físico y mental. Esta asociación es especialmente destacada en el caso enfermedades cardiovasculares y bajos niveles de optimismo. Sin embargo, los mecanismos por los que el optimismo se relaciona con mejores estados de salud aún no se han dilucidado.

El estudio descrito en el capítulo 2 se centra en la cuestión de si la longevidad de los padres está asociada con los niveles de optimismo de los hijos. En estudios anteriores se ha encontrado una asociación entre optimismo y longevidad, no sólo en individuos, sino que también en estudios familiares se ha demostrado que la longevidad de los padres está relacionada con las características psicológicas de los hijos. Para investigar esta asociación se utiliza un enfoque metodológico intergeneracional en el que se analiza el optimismo disposicional de los hijos en relación a la longevidad de los padres. Los resultados de este estudio muestran una asociación intergeneracional consistente entre la longevidad de los padres y el optimismo disposicional de los hijos. Este hallazgo apoya la hipótesis de que los factores hereditarios y factores ambientales (muy) tempranos que predisponen a algunas personas a niveles más altos

de optimismo probablemente también están vinculados a los que afectan a la longevidad.

En el capítulo 3 se exploran las asociaciones transversales y longitudinales entre un marcador del envejecimiento biológico – la longitud de los telómeros- y el optimismo disposicional. Estudios anteriores muestran una relación entre el acortamiento de los telómeros y un bajo bienestar mental en la edad adulta, pero se había investigado menos si esta asociación persistía en edades avanzadas. Los resultados de nuestro estudio no mostraron evidencia de una asociación entre la longitud de los telómeros y el optimismo en adultos mayores. Estos resultados contrastan con nuestra hipótesis de que menores niveles de optimismo estarían asociados con telómeros más cortos y acortamiento de los telómeros en edades avanzadas. Sin embargo, precisamente la edad avanzada de nuestra muestra puede haber dificultado la detección de una asociación debido a, por ejemplo, la mayor inestabilidad de la longitud de los telómeros en la vejez. En las personas mayores, la enzima telomerasa acorta y alarga los telómeros de manera más arbitraria, dificultando con ello el hallazgo de asociaciones con fluctuaciones en la longitud del telómero. Los estudios futuros que investiguen la asociación entre la longitud de los telómeros y el optimismo deberían, por lo tanto, tener en cuenta esta consideración.

En el capítulo 4 se describe el estudio de la proteína C reactiva (PCR) como uno de los muchos marcadores de inflamación crónica (en ausencia de infección) en relación con el optimismo. Debido a que la mayoría de estudios anteriores no estudian causalidad, en este estudio se analiza la asociación entre los haplotipos de PCR y los niveles de optimismo utilizando un diseño de aleatorización mendeliana, que permite inferir causalidad teniendo en cuenta factores distorsionantes no observados. Nuestros resultados no mostraron ninguna relación entre los haplotipos de PCR y los niveles de optimismo. Sin embargo, cuando se estratifica según el índice de masa corporal (IMC), se encuentra que los haplotipos de PCR que conducen a mayores niveles de PCR en plasma también se asocian con niveles más bajos de optimismo en las personas con sobrepeso u obesidad (es decir, con un IMC> 25 kg/m2). Estos hallazgos sugieren que los haplotipos de PCR que se relacionan con mayores niveles plasmáticos de PCR pueden estar relacionados causalmente con el optimismo disposicional y que esta asociación está, probablemente, modulada por el IMC. En otras palabras, la inflamación crónica puede afectar negativamente al optimismo en los sujetos obesos.

En el capítulo 5 se analiza la asociación entre la actividad física y el optimismo en una muestra de sujetos de edad avanzada con antecedentes de infarto de miocardio. Dado que tanto la inactividad física como el bajo optimismo son factores predictivos de pronóstico desfavorable en pacientes con enfermedad cardiovascular, la hipótesis que se formula es que ambos factores están estrechamente relacionados entre sí. Al inicio del estudio, los niveles más bajos de optimismo sólo están débilmente asociados con una menor actividad física. Sin embargo, no se encuentra ninguna asociación longitudinal a largo plazo. Estos resultados sugieren que la actividad física no afecta beneficiosamente los niveles de optimismo con el tiempo. Sin embargo, mayores niveles de actividad física sí que están estrechamente asociados con menos síntomas depresivos.

En los capítulos 6 y 7 se investiga la asociación entre el optimismo y factores psicosociales. En el capítulo 6 se describe la relación longitudinal entre el optimismo y la soledad. Dado que tanto los bajos niveles de optimismo como la soledad son determinantes de mala salud, es posible que el bajo optimismo esté estrechamente relacionado a la soledad. Además, la soledad puede explicar la asociación observada entre el bajo optimismo y la mala salud. Los resultados de nuestro estudio en hombres mayores muestran que niveles más altos de optimismo son factores pronósticos de una menor sensación de soledad durante 10 años de seguimiento, incluso

después de corregir el efecto de la variable distorsionante de la depresión. Nuestros hallazgos sugieren que los sujetos con bajos niveles de optimismo son más vulnerables a la soledad y, por lo tanto, podrían beneficiarse de una mayor atención clínica y de intervenciones destinadas a prevenir y aliviar la soledad. Por lo tanto, futuras intervenciones que mejoren el optimismo podrían ayudar a reducir los sentimientos de soledad en las personas mayores.

En el capítulo 7 se informa de los resultados de nuestro estudio sobre la relación transversal entre el optimismo y la imaginación mental. Las imágenes mentales, definidas como la experiencia de la percepción visual en ausencia de estímulos externos, están fuertemente relacionadas con la emoción y son consideradas una posible herramienta en la terapia cognitivo-conductual. Los primeros estudios con un período de seguimiento limitado (de dos semanas) han sugerido que es posible aumentar el optimismo a través de intervenciones dirigidas a promover la visualización positiva de los acontecimientos futuros. Nuestro estudio mostró una fuerte asociación transversal entre los niveles más altos de optimismo y la capacidad para visualizar imágenes mentales positivas. Estos resultados, aunque preliminares, sugieren que los optimistas pueden tener propiedades específicas en el uso de imágenes mentales y abren nuevas perspectivas futuras para la terapia cognitivo-conductual al sugerir un cambio de terapia verbal a ejercicios de entrenamiento visual para aumentar el optimismo.

Conclusiones

Los resultados presentados en esta tesis respaldan la hipótesis de que el optimismo está asociado a un mayor bienestar y longevidad, pero también indican que los niveles de optimismo intra-individuales son bastante estables en el tiempo y resistentes al cambio. Sin embargo, esta estabilidad del optimismo no implica necesariamente que las fluctuaciones en los niveles de optimismo no sean posibles. Ciertos acontecimientos vitales positivos o negativos probablemente provoquen pequeños cambios (transitorios) en nuestros niveles de optimismo. Sin embargo, también es posible que el optimismo disposicional no se pueda aprender y que los cambios sólo sean limitados en el que es un rasgo de la personalidad relativamente estable. Futuros estudios clínicos y epidemiológicos son necesarios para explorar los potenciales beneficios del optimismo. Pero ciertamente no estaría de más – e incluso podría dibujar una sonrisa en su rostro- ver el vaso medio lleno.

List of publications

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Curriculum Vitae

Nathaly Rius-Ottenheim was born on May 4th 1982, in Palma de Mallorca, Spain. After finishing secondary school with honors at Colegio La Salle in Palma, she started in 2000 her studies on Medicine at the Medical School of the University of Barcelona. After her graduation in 2006, she moved to Delft (the Netherlands) to start her professional career. In 2006 she started working as a medical resident at GGZ Delfland, a Psychiatry institution in Delft. In the summer of 2007 she attended the Aalborg Psychiatric Summer School (Denmark), where she followed specific courses on somatic disorders in psychiatric patients. In April 2008 she started her Psychiatry residency at the Leiden University Medical Centre (LUMC), with her first rotation at the department of Social Psychiatry at Rijnveste-Rivierduinen (Leiden). In October 2008, she started the work described in this dissertation at the department of Psychiatry of the LUMC, under supervision of Dr. E.J. Giltay, Prof. dr. F.G. Zitman, and Prof. dr. van der Mast. During her period as PhD student, she followed several courses (such as the Corsendonk course in Belgium) and attended national and international congresses in Maastricht, Santiago de Compostela, and San Francisco. In October 2011 she resumed her work as a Psychiatry resident.