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Psychological Wellbeing in Relation to Morbidity and Mortality Risk: Exploring Associations and Potential Mechanisms

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Declaration

I hereby declare that this thesis is of my own composition, and that it contains no material previously submitted for the award of any other degree. The work reported in this thesis has been executed by myself, except where due acknowledgement is made in the text. Versions of some of the chapters have been published as articles in scientific journals. The study described in chapter 2 was published in the April 2016 issue of *Psychosomatic Medicine* (Okely & Gale, 2016). The study described in chapter 3, into the association between wellbeing and arthritis incidence was published in the January 2016 issue of *Annals of Behavioral Medicine* (Okely, Cooper, & Gale, 2016) The other study described in chapter 3 into the association between wellbeing and chronic lung disease incidence was published in the July 2017 issue of *PloS ONE* (Okely, Shaheen, Weiss, & Gale, 2017). The study described in chapter 4 has been accepted for publication in *Psychosomatic Medicine* (Okely, Weiss, & Gale, 2017c). The study described in chapter 5 was published in the July 2017 issue of the *Journal of Behavioral Medicine* (Okely, Weiss, & Gale, 2017a). Finally the study described in chapter 6 will be published in the September 2017 issue of the *Journal of Psychosomatic Research* (Okely, Weiss, & Gale, 2017b).

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Lay Summary

The term psychological wellbeing describes the extent to which a person feels happy, fulfilled and in control of their life. People that report high wellbeing also tend to live longer and have a lower risk of developing some chronic physical diseases. In this thesis, we addressed three questions related to this association. Firstly, we tested whether high wellbeing was related to a lower risk of developing specific chronic diseases. Secondly, we examined which factors might help explain why wellbeing was associated with a lower risk of chronic disease. Thirdly, we tested whether the strength of association between higher wellbeing and longer life expectancy was affected by cultural differences or the experience of psychological stress. Chapter 1 provides an overview of research into associations between wellbeing and physical health. In addition, we describe theories of how the experience of high wellbeing might impact physical health. In chapters 2 and 3, we build on research into wellbeing and chronic physical disease risk by testing whether the association between wellbeing and disease risk is similar across different types of chronic disease. We found particularly strong associations between higher wellbeing and lower risk of arthritis, diabetes or chronic lung disease. In chapter 4, we further explore the association between wellbeing and arthritis risk. Specifically, we tested whether the association between wellbeing and arthritis risk was explained by inflammatory processes. We found that this association was partly explained by the fact that people with higher wellbeing tended to have lower blood levels of the inflammatory marker C-reactive protein which decreased their risk of developing arthritis. In chapter 5, we examined whether the association between higher

wellbeing and longer life expectancy was the same in different cultures. We looked at this association in individualist cultures – where people focus more on their personal interests – and collectivist cultures – where group interests are seen as more important. We found that the association between wellbeing and lower risk of death from cardiovascular disease was stronger in more individualistic cultures. In chapter 6, we tested the theory that the experience of happiness (which is considered part of psychological wellbeing) may be most strongly related to health under stressful conditions. In support of this idea, we found that the link between being happy and living longer was stronger in people that also reported more stress. In the final chapter, we summarise our findings, discuss the limitations of our approach and make recommendations for future research.

Thesis Abstract

There is evidence of a prospective association between wellbeing and health outcomes including disease risk and longevity. The aim of this thesis was firstly to further explore whether wellbeing is a risk factor for specific chronic physical diseases, and secondly, to identify potential mediators and moderators of the association between wellbeing and disease risk or longevity. Chapter 1 provides an overview of research into associations between wellbeing and physical health. In addition, we outline theoretical models of how the experience of high wellbeing might impact physical health. In chapters 2 and 3, we build on research into wellbeing and chronic physical disease risk. In these chapters, we tested whether the association between wellbeing and disease risk was similar across different types of disease, and, whether different theoretical domains of wellbeing varied in their association with disease risk. We found particularly strong associations – that were not explained by demographic or health behaviour differences – between higher wellbeing and lower risk of arthritis, diabetes or chronic lung disease. In chapter 4, we further explore the association between wellbeing and arthritis risk using mediation analysis. Specifically, we tested whether this association was mediated by inflammatory biomarkers. We found that the biomarker C-reactive protein accounted for a small proportion of the association between wellbeing and a reduced risk of arthritis. The focus of the next two chapters was on potential moderators of the association between wellbeing and mortality risk. In chapter 5, we examined whether the association between higher wellbeing and lower mortality risk varied across individualist and collectivist cultures. We found a significant interaction between

individualism and wellbeing such that the association between wellbeing and risk of mortality from cardiovascular disease was stronger in more individualistic countries. In chapter 6, we examined how positive affect (a subdomain of wellbeing), interacted with another psychosocial factor, namely subjective stress. Here, we tested Pressman and Cohen's (2005) stress buffering hypothesis that positive affect may be most strongly related with health under stressful conditions. In support of this hypothesis, we found that the association between positive affect and all-cause mortality risk was stronger in people reporting higher stress. In the final chapter, we summarise our findings, discuss the limitations of our approach and make recommendations for future research.

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Note

To acknowledge the contributions of co-authors, ‘we’ will be used instead of ‘I’ throughout the chapters of this thesis.

Chapter 1: General Introduction

The idea that emotional experiences can have physical health consequences has been a pervasive one. Ackerknecht (1982) traces the origins of this idea back to the ancient Greek physician Galen, who classified the experience of unbalanced or strong emotions as a potential cause of physical disease. Galen's ideas around the psychogenesis of chronic physical disease were carried forward by physicians from the Middle Ages to the Renaissance and gained further popularity among French and German scholars such as Philippe Pinel and Christoph Wilhelm Hufeland in the 19th century (Ackerknecht, 1982). Today, the influence of this research tradition is apparent in academic as well as popular culture – as evidenced by the multitude of papers, self-help books and popular magazines on the topic of emotion and health (Pressman & Cohen, 2005). In the academic realm, although the relationship between emotion and health is not yet fully understood, there have been significant advances. Specifically, the recent advent of large scale longitudinal studies that measure both emotion and long-term health outcomes, has enabled researchers to empirically test for an association between these variables (Berkman, Kawachi, & Glymour, 2014).

To date, research in this area has predominantly focused on the link between negative emotional states, such anxiety or depression, and physical health. Findings from longitudinal studies indicate that people who experience negative psychological states are at a higher risk of various adverse health outcomes. In a meta-analysis of studies into depression and risk of all-cause mortality, individuals diagnosed with depression had a 46% increased risk of mortality (Cuijpers & Smit, 2002). In a study

– using data from 10 large prospective cohort studies – into the association between psychological distress and cause-specific or all-cause mortality, Russ et al. (2012) found a positive dose-response relationship between psychological distress and risk of all-cause mortality, mortality from cardiovascular disease or external causes. Psychological distress was also associated with risk of mortality from cancer, but only at high levels of psychological distress (Russ et al., 2012). Depression has also been linked to a higher risk of incident type 2 diabetes (Mezuk, Eaton, Albrecht, & Golden, 2008), cardiovascular disease (Van der Kooy et al., 2007) and disability (Ericsson et al., 2002; Kivelá & Pahkala, 2001). Importantly, many of these studies (Kivelá & Pahkala, 2001; Mezuk et al., 2008; Russ et al., 2012; Van der Kooy et al., 2007) were able to rule out reverse causation (poor health impacting negative affect) as an explanation and thus provide evidence that negative emotional experience predicts future health risk.

The finding that negative affect may have deleterious health consequences has inspired researchers interested in positive emotions to test the opposite effect; namely, whether positive affect or wellbeing is associated with favourable health outcomes. Interest in this question stems from the idea that wellbeing and depressive symptoms represent qualitatively different constructs – both of which may be independently associated with health. The aim of this thesis is to further explore the association between wellbeing and chronic disease or mortality risk. In this introductory chapter, we first review definitions and measures of wellbeing. We then summarize evidence of an association between wellbeing and disease or mortality risk. We go on to

discuss mechanistic models that describe potential pathways linking wellbeing with health, and finally, we provide an overview of the research carried out for this thesis.

Defining wellbeing

Within the last decade, the construct of wellbeing has attracted much interest across the social sciences. In psychology, this interest follows the rise in popularity of positive psychology – a movement concerned with optimal psychological functioning (Seligman & Csikszentmihalyi, 2014). Within political and economic fields, measures of societal wellbeing have been developed in response to criticisms of development classifications based purely on income (Forgeard, Jayawickreme, Kern, & Seligman, 2011). However, despite the popularity of wellbeing research, there is a lack of consensus regarding how wellbeing should be defined and measured (Dodge, Daly, Huyton, & Sanders, 2012).

Debate regarding the definition of wellbeing has been informed by two distinct theoretical perspectives (Dodge et al., 2012). The hedonic approach emphasises the experience of positive emotion and mood such as pleasure or happiness. The eudemonic perspective defines wellbeing in relation to positive functioning and self-realization. Wellbeing is now generally recognized as being a multidimensional construct that incorporates both hedonic and eudemonic traditions (Diener, Scollon, & Lucas, 2009) However, the number of dimensions that make up wellbeing is still debated.

In this thesis, the term wellbeing is used to describe a multidimensional construct consisting of two main subdomains: hedonic and eudemonic wellbeing. In lay terms,

these domains are often described as ‘feeling good’ and ‘functioning well’. Here, we define hedonic wellbeing as the experience of positive emotions. These can include emotions with high arousal (e.g., excitement or joy) and low arousal (e.g., feeling relaxed). In line with the classification outlined by Waterman (1993), we define eudemonic wellbeing as living fully to one’s potential and values. Indicators of eudemonic wellbeing such as life meaning or purpose may result in neutral or even negative affect in the short term, but ultimately promote positive cognitive appraisals and emotions (Hernandez et al., 2017). It should be noted that the definition of eudemonic wellbeing adopted here, is less explicit than some others; for instance, Ryff and Singer (1998) posit that eudemonic wellbeing can be defined in terms of autonomy, personal growth, self-acceptance, life purpose, mastery, and positive relatedness. We argue that while these attributes are likely to foster wellbeing, other factors may also play a role, depending on a person’s culture, life stage or experience. This contention is discussed in more detail in chapters 5 and 7.

Some authors suggest that wellbeing consists of additional constructs which are not easily categorised as hedonic or eudemonic; these include optimism, hope (Hernandez et al., 2017) and life-satisfaction (Martín-María et al., 2017). While optimism and hope are associated with experiences of hedonic and eudemonic wellbeing (Magaletta & Oliver, 1999; Scheier & Carver, 1992), we will consider these factors as potential predictors rather than indicators of wellbeing. Ultimately, these constructs represent attributional styles, and as such are more closely linked to personality than wellbeing. The construct of life-satisfaction is more complicated as it arguably reflects elements of hedonic as well as eudemonic wellbeing. Martín-

María et al. (2017) suggest that life-satisfaction should be considered as a third 'evaluative' subdomain of wellbeing. It is useful to make this distinction; however, the measures employed in this thesis, described below, categorise life satisfaction as a component of hedonic wellbeing.

Although we distinguish between hedonic and eudemonic wellbeing, some authors have argued that different wellbeing measures are likely to yield a similar pattern of results (Chida & Steptoe, 2008; Diener & Chan, 2011; Howell, Kern, & Lyubomirsky, 2007). This is because wellbeing constructs are generally highly correlated (Howell et al., 2007). For instance, although hedonic and eudemonic aspects of wellbeing are theoretically separable, they are strongly related – an individual reporting high eudemonic wellbeing is also likely to experience high positive affect and *vice versa* (Howell et al., 2007; Kashdan, Biswas-Diener, & King, 2008). In support of this argument, studies exploring the factor structure of wellbeing constructs typically find a single higher order factor (Jovanović, 2015; Longo, Coyne, Joseph, & Gustavsson, 2016; Lyubomirsky, Sheldon, & Schkade, 2005; Ryff & Keyes, 1995; Stones & Kozma, 1985). Although, others have found support for two distinct but correlated factors consisting of hedonic and eudemonic wellbeing (Linley, Maltby, Wood, Osborne, & Hurling, 2009). Additionally, there is evidence that these subdomains have some different predictors. While hedonic wellbeing is largely predicted by present circumstances, and the fulfilment of needs and desires, eudemonic wellbeing is more closely related to activities of self-expression, helping others and an orientation to one's past and future (Baumeister, Vohs, Aaker, & Garbinsky, 2013).

A second question regarding the nature of wellbeing relates to the stability of the construct. Early research into the treadmill hypothesis, that is, the idea people return to a set point of happiness following positive or negative experiences, suggests that happiness changes little over time and is unaffected by significant life events (Brickman, Coates, & Janoff-Bulman, 1978). However, others have documented how some experiences, such as unemployment (Lucas, Clark, Georgellis, & Diener, 2004) or loss of a partner (Lucas, Clark, Georgellis, & Diener, 2003), can lead to long-term changes in wellbeing. It should be noted that these findings are predominantly based on hedonic measures of wellbeing (Vanhoutte, 2012); less is known regarding trajectories of eudemonic wellbeing over time. Considering hedonic and eudemonic wellbeing are highly correlated, one might expect the two constructs to change in similar ways. However, Waterman (2007) suggests that eudemonic wellbeing may be characterised by a distinct trajectory. Specifically, he suggests that with age, people develop skills and resources that allow them to realise their potential, and thus, achieve greater eudemonic wellbeing. Waterman (2007) likens this gradual increase over time to a 'eudemonic staircase'.

A further issue of contention within the field of wellbeing research is whether wellbeing and depression (or negative affect) represent opposite ends of a continuum of psychological functioning – the bipolar model – or whether these constructs are best considered as independent processes – the two factor model (Reich, Zautra, & Davis, 2003). There is evidence for the bipolar and the two-factor model. In support of the former, a number of authors have argued that the negative correlation between wellbeing and depression is best described by a bipolar model (Green, Salovey, &

Truax, 1999; Remington, Fabrigar, & Visser, 2000; Russell & Carroll, 1999; Zevon & Tellegen, 1982). In addition, studies that assessed momentary experiences of positive affect (a component of wellbeing) and negative affect found that, at the within-person level, high positive affect is generally accompanied by the experience of low negative affect and *vice versa* (Napa Scollon, Diener, Oishi, & Biswas-Diener, 2005; Yik, 2007). Finally, results from a genome wide association study indicate that there is a high genetic correlation between subjective wellbeing and depression (r_g = -0.75) (Okbay et al., 2016). This finding suggests that there are some shared biological pathways that influence both wellbeing and depression.

In support of the two factor model, there is evidence that positive and negative affect can co-occur (J. T. Larsen, Hershfield, Stastny, & Hester, 2016). In addition, wellbeing and depressive symptoms are correlated with some different neuroendocrine and cardiovascular biomarkers (Ryff et al., 2006). Finally, there is evidence that positive and negative affect differ etiologically. A recent twin study found that individual differences in average negative affect were significantly heritable, whereas individual differences in average positive affect were not (Zheng, Plomin, & von Stumm, 2016). Individual differences in positive affect were largely explained by environmental differences in this study.

The nature of the relationship between wellbeing and depressive symptoms has implications for research into wellbeing and health. If high wellbeing represents the opposite of depression, then associations between wellbeing and physical health could simply reflect the absence of negative affect or depressive symptoms (Reich et al., 2003). The prospective association between depression and morbidity or

mortality risk is well established (Barth, Schumacher, & Herrmann-Lingen, 2004; Cuijpers & Smit, 2002; M. Pinquart & Duberstein, 2010). However, if high wellbeing and depressive symptoms represent different constructs, then wellbeing could impact health independently of negative affect. In support of this latter view, meta-analytic studies into the association between wellbeing and mortality risk indicate that the association is partially independent of depressive symptoms (Chida & Steptoe, 2008; Diener & Chan, 2011; Martín-María et al., 2017).

Measuring wellbeing

Methods for measuring wellbeing are numerous and reflect the various perspectives regarding the nature of this construct. Approaches include self-report questionnaires, momentary based wellbeing assessments (for example, see Steptoe, Gibson, Hamer, & Wardle, 2007) and more qualitative assessments (Camfield, Crivello, & Woodhead, 2009).

The studies described in this thesis employ self-report measures of wellbeing. In the studies described in chapters 2 to 5, wellbeing was assessed with the CASP-19 quality of life questionnaire (Hyde, Wiggins, Higgs, & Blane, 2003) or the CASP-12, which is an abridged version of the CASP-19. The CASP-19 was developed to assess wellbeing in older populations. The questionnaire is based on a 'needs satisfaction' model of wellbeing. According to this model, the experience of wellbeing is dependent on the satisfaction of four specific needs. Much like Maslow's (1962) needs satisfaction model, the needs that underlie wellbeing are believed to be universal. They are: control (the ability to intervene in one's environment), autonomy (freedom from unwanted interference from others), self-realisation (self-acceptance

and life purpose) and pleasure (the experience of positive affect). These four domains can also be grouped into measures of eudemonic wellbeing (control, autonomy and self-realisation) and hedonic wellbeing (pleasure). In the study described in chapter 6, we employed a measure of positive affect taken from the positive affect subscale of the General Wellbeing Questionnaire (GWQ) (Fazio, 1977). The GWQ positive affect subscale is a measure of hedonic wellbeing. Both the CASP measures and the positive affect measure were designed to assess wellbeing at the trait level, that is, how an individual feels generally (or over the past month) rather than how they feel in the moment when wellbeing is assessed. See tables 1.1-1.3 for a summary of items in the CASP-19, CASP-12 and the GWQ positive affect subscale.

Table 1.1

CASP-19 items and subdomains

Subdomain	**Items** [a]
Control	1. My age prevents me from doing the things I would like to do
	2. I feel that what happens to me is out of my control
	3. I feel free to plan for the future
	4. I feel left out of things
Autonomy	5. I can do the things I want to do
	6. Family responsibilities prevent me from doing the things I want to do
	7. I feel that I can please myself what I do
	8. My health stops me from doing the things I want to do
	9. Shortage of money stops me from doing things I want to do
Pleasure	10. I look forward to each day
	11. I feel that my life has meaning
	12. I enjoy the things that I do
	13. I enjoy being in the company of others
	14. On balance, I look back on my life with a sense of happiness
Self-realization	15. I feel full of energy these days
	16. I choose to do things that I have never done before
	17. I feel satisfied with the way my life has turned out
	18. I feel that life is full of opportunities
	19. I feel that the future looks good for me

[a] Response options: ‘often’, ‘sometimes’, ‘not often’, and ‘never’.

Table 1.2

CASP-12 items and subdomains

Subdomain	**Items** [a]
Control	1. My age prevents me from doing the things I would like to do
	2. I feel that what happens to me is out of my control
	3. I feel left out of things
Autonomy	4. I can do the things I want to do
	5. Family responsibilities prevent me from doing the things I want to do
	6. Shortage of money stops me from doing things I want to do
Pleasure	7. I look forward to each day
	8. I feel that my life has meaning
	9. On balance, I look back on my life with a sense of happiness
Self-realization	10. I feel full of energy these days
	11. I feel that life is full of opportunities
	12. I feel that the future looks good for me

[a] Response options: 'often', 'sometimes', 'not often', and 'never'.

Table 1.3

Positive affect subscale of the General Wellbeing Questionnaire

Items	**Anchors**
1. How have you been feeling in general in the past month?	In excellent spirits/In very low spirits
2. How happy, satisfied, or pleased have you been with your personal life, during the past month?	Very happy/Very dissatisfied
3. How much energy, pep, vitality have you felt, during the past month?	Very energetic/No energy at all

Associations between wellbeing and disease or mortality risk

The finding that wellbeing is positively associated with longevity is well established. In a meta-analysis of longitudinal studies into the association between hedonic, eudemonic or evaluative wellbeing and longevity, Martín-María et al. (2017) found that all three domains of wellbeing were associated with a lower mortality risk. The strength of this association was similar and also significant in analysis of a subgroup of studies (n = 24) that controlled for health status, socioeconomic status, presence of depressive or anxiety symptoms and smoking – suggesting that the association between wellbeing and mortality risk is partially independent of these established risk factors. The pooled hazard ratio (HR), which was treated as an effect size measure, for this analysis was 0.88 (95% confidence interval [CI] = 0.83-0.94). Similar findings have been reported in meta-analyses of studies into the association between positive affect or life purpose, and risk of all-cause mortality (R. Cohen,

Bavishi, & Rozanski, 2016; Y. Zhang & Han, 2016). In addition to studies of mortality risk, prospective cohort studies have documented associations between higher wellbeing and lower risk of incident cardiovascular disease (Feller, Teucher, Kaaks, Boeing, & Vigl, 2013; Sin, 2016), cancer (Feller et al., 2013; Wakai et al., 2007) and type 2 diabetes (Feller et al., 2013; Shirom, Toker, Melamed, Berliner, & Shapira, 2012).

Although the number of studies documenting an association between wellbeing and disease or mortality risk is impressive, results should be interpreted with caution. In their meta-analysis into the association between wellbeing and mortality risk, Martín-María et al. (2017) found evidence that studies documenting a protective effect of wellbeing were more likely to be published than studies with null findings. In addition, studies with smaller sample sizes found stronger associations between wellbeing and longevity. Thus, current estimates of the strength of association between wellbeing and longevity in published papers may be inflated. In addition, some studies have found no evidence of a direct association between wellbeing and longevity. Most notably, in a study of 719, 671 British women, Liu et al. (2016) found that, following adjustment for history of chronic disease and self-rated health, happiness was not associated with mortality risk. The decision to adjust for self-rated health in this study has attracted some criticism. Wellbeing and self-rated health are highly correlated; thus, while adjusting for self-rated health reduces the risk of reverse causality (i.e. health status impacting wellbeing), this approach increases the risk of statistical over adjustment (Stringer & Veldkamp, 2016).

Finally, it should be noted that there are limitations inherent to observational longitudinal studies that make conclusions regarding a causal association between wellbeing and disease risk or longevity problematic (Steptoe, Deaton, & Stone, 2014). Specifically, it is impossible to rule out the effect of all potential confounding factors or the effect of reverse causality (an individual's physical health status impacting on their sense of wellbeing). Randomised controlled trails in which individuals are assigned to a wellbeing intervention, such as mindfulness (Keng, Smoski, & Robins, 2011), would help resolve these issues (Hernán & Taubman, 2008). However, such large scale studies have not yet been conducted (Sin, 2016).

Pathways from wellbeing to health

The finding that the association between wellbeing and longevity is not fully explained by demographic differences, health status or differences in negative affect (Chida & Steptoe, 2008; Martín-María et al., 2017), has prompted researchers to consider additional mechanisms that could account for this association. In a seminal review, Pressman and Cohen (2005) outlined two compatible models that might account for the association between positive affect and health: the main effect model and the stress buffering model. According to the main effect model, the experience of positive affect impacts directly on physiological processes and health behaviours associated with good health. The stress buffering model, on the other hand, proposes that positive affect promotes good health by protecting against the pathogenic consequences of psychological stress. Although the direct effect and stress buffering models describe associations specifically between positive affect (hedonic wellbeing) and health, these models have since been applied more generally in explaining

associations between various wellbeing measures (including eudemonic wellbeing) and health outcomes (e.g. Ong & Patterson, 2016).

Findings from multiple studies support the associations outlined in Pressman and Cohen's (2005) models. Firstly, according to the main effect model, one pathway by which wellbeing could influence health is by impacting health practices. In support of this idea, longitudinal and cross-sectional studies have documented associations between higher wellbeing or positive affect and higher levels of physical activity (Garcia, Archer, Moradi, Andersson-Arntén, & others, 2012; E. S. Kim, Kubzansky, Soo, & Boehm, 2016). Others have found that wellbeing is positively associated with sleep quality (Steptoe, O'Donnell, Marmot, & Wardle, 2008) and diet (specifically, higher fruit intake and limited fat intake) (Grant, Wardle, & Steptoe, 2009). Individuals who report high wellbeing are also less likely to smoke (Grant et al., 2009; Steptoe, Dockray, & Wardle, 2009). To date, most studies in this area have been cross-sectional; thus, work is needed to establish the direction of causation between wellbeing and health behaviours. Steptoe et al. (2009) suggest that the association is likely bi-directional with health behaviours impacting wellbeing and the experience of wellbeing impacting subsequent lifestyle choices. Importantly, there is evidence to suggest that lifestyle differences only partially account for associations between wellbeing and health. Several longitudinal studies found that the association between wellbeing and mortality or disease risk remained significant after adjusting for health behaviours (Boehm, Peterson, Kivimaki, & Kubzansky, 2011; Chida & Steptoe, 2008; Feller et al., 2013).

A further mechanism suggested by Pressman and Cohen (2005) is that wellbeing may impact directly on physiological processes relevant to disease risk and longevity. Steptoe, Demakakos, de Oliveira and Wardle (2012) outlined this processes in more detail; specifically, they proposed that wellbeing may positively impact neuroendocrine and autonomic functioning via prefrontal and limbic system pathways. Over the long term, effective functioning of these systems may help reduce health risks and promote recovery from illnesses. Findings from studies into the association between wellbeing and psychobiological processes provide support for this theory. In a review of such studies, Dockray and Steptoe (2010) concluded that wellbeing impacts neuroendocrine, autonomic and immune systems independently of negative affect and that the magnitude of these effects is clinically significant. The authors also note that hedonic and eudemonic wellbeing may be related to distinct biological processes or impact the same process but in different ways. However, most studies into the biological correlates of wellbeing have used measures of hedonic rather than eudemonic wellbeing (Steptoe et al., 2012). Findings from the few studies that included both hedonic and eudemonic measures have been mixed. For instance, in a cross-sectional study of 135 women, higher eudemonic but not hedonic wellbeing was associated with lower levels of daily salivary cortisol, pro-inflammatory cytokines, cardiovascular risk, and longer duration REM sleep (Ryff, Singer, & Dienberg Love, 2004). By contrast, another cross-sectional study of 7,795 older men and women found similar associations between hedonic and eudemonic wellbeing and a range of biological measures including C-reactive protein, dehydroepiandosterone sulfate and plasma triglycerides (Steptoe et al., 2012).

An additional mechanism by which wellbeing might impact health is through enhancing social support – an established predictor of longevity (Holt-Lunstad, Smith, & Layton, 2010; Pressman & Cohen, 2005). Cross-sectional studies have found that people with high hedonic or eudemonic wellbeing are more likely to report closeness with family and friends and a greater sense of belonging in their community (Lyubomirsky, King, & Diener, 2005; Nguyen, Chatters, Taylor, & Mouzon, 2016; Ramsey & Gentzler, 2015; Theurer & Wister, 2010). A review of longitudinal studies found that the association between wellbeing and social connectedness is bi-directional; individuals with high hedonic or eudemonic wellbeing are more likely to develop and maintain positive relationships. Good social support, in turn, can lead to an increase in hedonic and eudemonic wellbeing (Ramsey & Gentzler, 2015). As few studies included both measures of hedonic and eudemonic wellbeing, it is unclear whether these domains of wellbeing are differentially related to social support. However, there is some evidence that quality of close relationships may impact levels of eudemonic wellbeing more than hedonic wellbeing. For instance, a longitudinal study found that romantic relationship quality predicted eudemonic but not hedonic wellbeing 10 years later (Selcuk, Gunaydin, Ong, & Almeida, 2016).

Although the main effects hypothesis has attracted greater research attention, some studies have tested for the mechanisms outlined in Pressman and Cohen's (2005) stress buffering model. That is, the idea that wellbeing reduces health risk by protecting against health harming behavioural and physiological responses to psychological stress. For instance, experimental studies have found that eliciting

positive affect (compared with an emotionally neutral condition) is associated with a reduced physiological stress response and quicker recovery following exposure to a laboratory stress task (Fredrickson, Mancuso, Branigan, & Tugade, 2000; Kraft & Pressman, 2012). In a cross-sectional study, Blevins, Sagui and Bennett (2016) found that the positive correlation between self-reported stress and elevated C-reactive protein, an inflammatory biomarker, was weaker among participants that also reported high levels of positive affect. There is also evidence that greater wellbeing is associated with positive lifestyle changes (e.g. adopting a healthy diet or exercising more frequently) following stressful life events such as diagnosis of chronic disease (Chaves & Park, 2015; Hawkins et al., 2010; Park, Edmondson, Fenster, & Blank, 2008).

Many of the biomarker and behavioural variables related to wellbeing are also related to other measures of positive functioning such as optimism or resilience. For instance, optimism, (which is positively correlated with wellbeing (Cheng & Furnham, 2001; J. Zhang et al., 2014)), has been negatively associated with levels of inflammatory biomarkers (Rasmussen, Scheier, & Greenhouse, 2009) and positively associated with health protective behaviours including physical activity (Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004). Further work is needed to outline the relationship between wellbeing, personality traits and other measures of resilience, and, to test whether these constructs are differentially related to health processes. Only a few studies have addressed this issue. Cohen, Alper, Doyle, and Treanor (2006) found that adults who reported higher levels of hedonic wellbeing were less likely to become ill following experimental exposure to rhinovirus, and,

that this association was partially independent of optimism, extraversion, mastery and self-esteem. In another study, participants with higher hedonic wellbeing were characterised by a larger antibody response to a hepatitis B vaccination (Marsland, Pressman, & Cohen, 2007). The association between hedonic wellbeing and antibody response was mostly independent of optimism and extraversion.

Although there is some evidence that hedonic wellbeing is related to physiological responses independently of other related psychological constructs including optimism and extraversion. Marsland, Pressman and Cohen (2007) suggest that personality and coping styles are likely to influence an individual's sense of hedonic wellbeing, which in turn impacts physiological processes. A similar model is proposed by Friedman and Kern (2014), the authors suggest that pathways to health and longevity originate with genetic predispositions, environmental factors and personality traits, and are mediated by lifestyle patterns and subjective wellbeing. See figure 1.1 for a summary of this model.

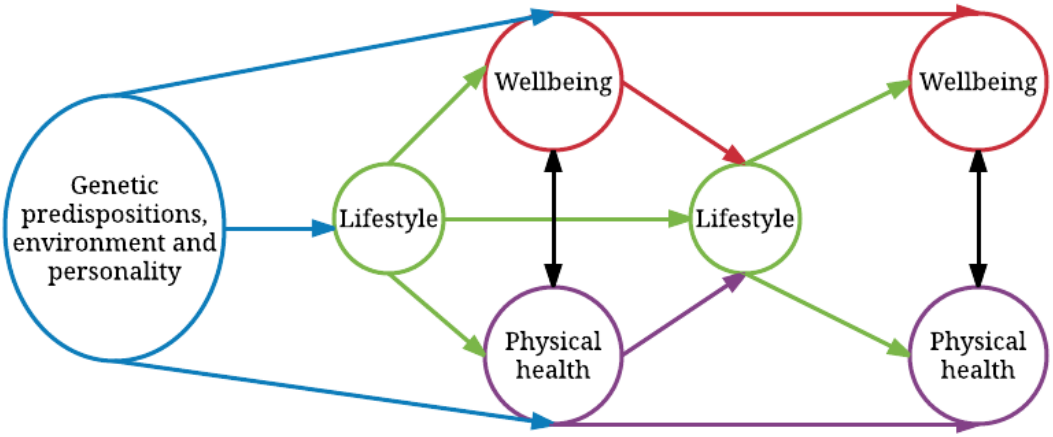

Figure 1.1

Model of the relationships between wellbeing, personality and health (Friedman & Kern, 2014)

Research aims

In a recent review of studies into the link between positive affect and health, Cross and Pressman (2017) conclude that there is now evidence of the mechanisms outlined by the main effects and stress buffering hypotheses. The authors suggest that the processes outlined in these models are likely to jointly impact health outcomes. As highlighted in our discussion of these mechanisms, associations between wellbeing, health behaviours and physiological functioning are likely bi-directional. These reciprocal relationships have been described by some as an upward spiral – whereby mutual increases in wellbeing and factors beneficial to health – result in a positive health and wellbeing trajectory over the life course (Ramsey & Gentzler, 2015).

Ultimately, research into wellbeing as a predictor of health is motivated by the idea that wellbeing interventions could provide an additional method of health promotion (Diener & Chan, 2011; Howell et al., 2007). Developing such interventions will require a clear understanding of the pathways linking wellbeing and health. Currently, there is evidence of a prospective association between wellbeing and longevity or the risk of some chronic diseases including cardiovascular disease (Feller et al., 2013; Sin, 2016), cancer (Feller et al., 2013; Wakai et al., 2007) and type 2 diabetes (Feller et al., 2013; Shirom et al., 2012). Researchers have begun to explore potential mediators of these associations. However, our understanding of the association between wellbeing and health is still limited.

The aim of this thesis was to further clarify the nature of the association between wellbeing and disease or mortality risk. As the studies described in this thesis were observational, we could not directly test for a causal association between wellbeing and these outcomes. However, we were able to address a number of other unanswered questions. Firstly, it is currently unclear whether the association between wellbeing and disease risk is similar across different types of disease. In chapters 2 and 3 we addressed this question by comparing associations across a range of physical chronic diseases. Secondly, there are numerous psychosocial, behavioural and physiological pathways that could account for the association between wellbeing and disease risk (Pressman & Cohen, 2005). However, the relative contribution of these mechanisms is not clear (Cross & Pressman, 2017). In chapters 2 and 3, we additionally examined the extent to which health behaviours or demographic differences accounted for associations between wellbeing and disease risk. In chapter

4 we extended this line of investigation by testing the extent to which inflammatory processes mediate the association between wellbeing and arthritis risk. Finally, the strength of the association between wellbeing and health could be moderated by individual differences and environmental factors. Previous work indicates that gender moderates the association between wellbeing and mortality risk (Howell et al., 2007; Martín-María et al., 2017) and age moderates the association between wellbeing and cardiovascular or physiological reactivity (Howell et al., 2007). However, the effect of other potential moderators remains to be explored. In chapter 5, we considered the role of culture as a potential moderator. Here, we examined whether the association between wellbeing and mortality risk varied across individualist and collectivist cultures. In chapter 6, we examined how wellbeing interacted with another psychosocial factor, namely subjective stress. In this study, we tested Pressman and Cohen's (2005) stress buffering hypothesis that wellbeing may be most strongly related with health under stressful conditions.

Chapter 2: Wellbeing and Chronic Disease Incidence

Introduction

Research indicates that wellbeing is inversely associated with the risk of some chronic diseases. High wellbeing has been related to lower incidence of cancer and breast cancer specifically (Feller et al., 2013; Wakai et al., 2007), type 2 diabetes (Feller et al., 2013; Shirom et al., 2012) and cardiovascular diseases (Boehm et al., 2011; Giltay et al., 2004; Koizumi, Ito, Kaneko, & Motohashi, 2008; Kubzansky, Sparrow, Vokonas, & Kawachi, 2001). These associations are not fully explained by lifestyle or demographic differences. Additionally, findings from studies that controlled for depression, indicate that this negative psychosocial factor does not fully account for the association between wellbeing and risk of cardiovascular disease or type 2 diabetes (Boehm et al., 2011; Kubzansky et al., 2001; Shirom et al., 2012). However, evidence of a link between wellbeing and disease risk is inconsistent, other studies found no relation between wellbeing and disease incidence, specifically, in the case of breast cancer (Lillberg et al., 2002) and heart disease (Feller et al., 2013; Koizumi et al., 2008; Nabi, Kivimaki, Vogli, Marmot, & Singh-Manoux, 2008).

The study described in this chapter, built on previous findings by addressing three research objectives. Firstly, chronic diseases share a number of common risk factors (such as sedentary behaviour or unhealthy diet) but it is unclear whether chronic diseases share another risk factor in the form of wellbeing. Richman et al. (2005) have argued that wellbeing may provide a 'broad base of resilience' against chronic disease. However, Diener and Chan (2011) suggest that as different types of disease

involve different physiological processes and causes, it is likely that the strength of association between wellbeing and disease risk will vary across different types of diseases – with some having little or no association with levels of prior wellbeing.

Currently, research into the association between wellbeing and multiple disease outcomes is limited. Richman et al. (2005) examined the association between positive emotions (hope and curiosity) and risk of respiratory tract infection, diabetes and hypertension. After controlling for health behaviours and demographic differences, the authors found that positive emotions were associated with incident hypertension but not with incident diabetes or respiratory tract infection (Richman et al., 2005). However, it is unclear whether wellbeing was differentially related to these disease outcomes as the study was underpowered (n = 1,041). Previously reported effect sizes of the association between wellbeing and disease risk have been small; for instance, in a longitudinal study into life-satisfaction and diabetes risk, a standard deviation increase in life satisfaction score was associated with a 15% reduction in diabetes risk (HR: 0.85; 95% CI: 0.76-0.95), following adjustment for demographic factors. Feller et al. (2013) conducted a larger study (n = 50,358) into the prospective association between life-satisfaction and risk of type 2 diabetes, myocardial infarction, stroke, and cancer. In women, lower life satisfaction was associated with a higher risk of cancer, diabetes and stroke but not myocardial infarction. Following adjustments for health behaviours, demographic factors and prevalent diseases, participants in the lowest tertile compared to the highest tertile of life satisfaction, had a higher risk of cancer (HR: 1.45; 95% CI: 1.18-1.78) and stroke (HR: 1.69; 95% CI: 1.05-2.73). However, the association between life satisfaction

and diabetes risk was no longer significant. In men, lower life satisfaction was associated with a lower risk of stroke (HR: 1.60; 95% CI: 1.02-2.49). However, this association was not significant following adjustment for health behaviours and prevalent diseases.

We built on this previous work by comparing the association between wellbeing and disease risk across a greater number of chronic diseases. We examined the association between wellbeing and risk of stroke, heart attack, diabetes, cancer, arthritis and chronic lung disease. As noted above, previous studies have found associations between wellbeing and risk of cardiovascular disease (Boehm et al., 2011; EJ et al., 2004; Koizumi et al., 2008; Kubzansky et al., 2001), type diabetes 2 (Feller et al., 2013; Shirom et al., 2012) and cancer (Feller et al., 2013; Wakai et al., 2007); however, associations between wellbeing and risk of arthritis or chronic lung disease remain to be explored.

The second objective of this study was to test whether eudemonic and hedonic measures of wellbeing are differentially associated with disease risk. Eudemonic wellbeing is defined in terms of self-realization, sense of autonomy and meaning, whereas hedonic wellbeing is defined as the experience of positive emotion and mood such as pleasure or happiness. Both dimensions of wellbeing have been linked to longevity and risk of cardiovascular disease (Boehm et al., 2011; Chida & Steptoe, 2008; Davidson, Mostofsky, & Whang, 2010; Martín-María et al., 2017; Ong & Patterson, 2016); however, there is some indication that eudemonic wellbeing may be more closely related to physical health than hedonic wellbeing. For instance, in a study into mortality risk, following adjustment for established risk factors, measures

of eudemonic wellbeing (control and self-realisation) but not hedonic wellbeing (pleasure) were associated with mortality risk (Netuveli, Pikhart, Bobak, & Blane, 2012). Similarly, in a cross sectional study, eudemonic but not hedonic wellbeing was associated with biomarkers of neuroendocrine, immune and cardiovascular health (Ryff et al., 2004).

There are numerous psychosocial, behavioural and physiological pathways that could account for the association between wellbeing and disease risk (Pressman & Cohen, 2005). However, the relative contribution of these mechanisms is not clear (Cross & Pressman, 2017). Thus, the final objective of this study was to examine the extent to which health behaviours, depressive symptoms or demographic differences account for associations between wellbeing and disease risk.

Methods

Study population

The English Longitudinal Study of Ageing is a prospective cohort study developed with the view of understanding the processes involved in the transition from retirement into old age. The study follows a representative sample of men and women aged 50 or over living in England. Participants were initially recruited from the Health Survey for England database in 1998, 1999 and 2001. At wave 1 (2002-3) 12,099 people participated; since then, participants have been interviewed biennially. Ethical approval was provided by the London Multicentre Research and Ethics Committee. All participants gave written informed consent (Steptoe, Breeze, Banks, & Nazroo, 2013).

Wellbeing

Wellbeing at wave 1 was assessed with the CASP-19 quality of life questionnaire (Hyde et al., 2003). Participants respond to 19 questions on a four point Likert scale (scored 0-3). Possible scores range from 0-57 with higher scores indicating higher levels of wellbeing. For those individuals with 4 or fewer CASP-19 items missing, we imputed a score for the missing items based on their mean score for the completed items. For the study sample, internal consistency for CASP-19 scores was high ($\alpha = 0.87$). In addition to providing an overall score, the CASP-19 is designed to measure wellbeing across the four sub-domains of control (the ability to intervene in one's environment), autonomy (freedom from unwanted interference), self-realisation (self-acceptance and life purpose) and pleasure (enjoyment in life). For the study sample, Cronbach's alpha scores for the subdomains of control, autonomy, self-realisation and pleasure were 0.60, 0.52, 0.82 and 0.78 respectively.

We also created a modified wellbeing measure for use in sensitivity analysis. This measure excluded responses to the health related item in the CASP-19: 'my health stops me from doing the things I want to do'.

Chronic disease incidence

At wave 1, participants were asked whether a doctor had ever told them that they had any of the following conditions: 'high blood pressure/hypertension', 'heart attack', 'diabetes or high blood sugar', 'a stroke', 'chronic lung disease', 'arthritis or rheumatism', 'or cancer'. Participants reported the month and year of their diagnosis. In subsequent waves (2-5) participants were presented with the same list and asked whether they had been diagnosed with any of the listed conditions since their last

interview. If a new diagnosis was reported, participants reported the month and year of their diagnosis. Data regarding date of diagnosis was not available for chronic lung disease. Instead, time of diagnosis was indexed as the time of the interview (month and year) at which the participant first reported a diagnosis of chronic lung disease.

Covariates

We chose age, gender, depressive symptoms, socio-economic status – as indexed by household wealth, level of education and relationship status as potential confounders and health behaviours (physical activity, alcohol consumption and smoking status) and body mass index (BMI) as potential mediators of the relationship between wellbeing and disease incidence. Feller et al. (2013) found that adjusting for health behaviours, BMI and education attenuated the association between life satisfaction and disease incidence. Socio-economic status, depressive symptoms and age have been associated with wellbeing as well as incidence of chronic disease (Brett et al., 2012; Dalstra et al., 2005; Eaton, Armenian, Gallo, Pratt, & Ford, 1996; Penninx et al., 1998; Martin Pinquart & Sörensen, 2000; Steptoe et al., 2014; Strong, Mathers, Leeder, & Beaglehole, 2005).

The eight item version of Centre for Epidemiological Studies Depression Scale (CES-D) was used to assess symptoms of depression (Steffick, 2000). Socioeconomic status was indexed by total household wealth, including savings and investments, value of any property or business assets, net of debt, excluding pension assets. Household wealth has been identified as the most accurate indicator of long-term socioeconomic circumstances in ELSA (Banks et al., 2003). The study sample

was divided into quintiles according to total household wealth. Education was categorised based on highest reported level of qualification (less than O-level or equivalent, O-level or equivalent, A-level or equivalent, higher than A-level but below degree and degree level). Relationship status was dichotomised as having a partner (yes or no). Participants reported the frequency with which they engaged in vigorous, moderate and mild exercise. Response options were 'more than once a week', 'once a week', 'one to three times a month' and 'hardly ever or never'. As previously (Hamer, de Oliveira, & Demakakos, 2014), responses were dichotomised based on exercise frequency – either once a week (or more) or less than once a week. Responses were then summed to create four categories: physical inactivity, mild but not moderate or vigorous activity at least once a week, moderate but not vigorous physical activity at least once a week and vigorous physical activity at least once a week. Frequency of alcohol consumption in the last 12 months was recorded. Participant response options were: 'twice a day or more', 'daily or almost daily', 'once or twice a week', 'once or twice a month', 'special occasions only' and 'not at all'. Responses were scored on a 6-point scale. Participants reported their smoking status as: 'non-smoker', 'former smoker' or 'smoker'. Apart from BMI, all covariate measures were recorded at wave 1. BMI data was recorded at wave 0 which took place in 1998, 1999 and 2001.

Analytical sample

Of the 12,099 people taking part in wave 1, we included 8,182 in the current analysis. Participants were excluded if they only took part in wave 1 (n = 2,121); they were additionally excluded if they had incomplete (missing more than 4 items)

or missing data for wellbeing (n = 886) and further excluded if they had missing data on any of the covariate variables (n = 910). The median length of follow up was 6 years; the last year of assessment considered in this study was 2011.

Main analysis

Analyses were performed in IBM SPSS version 22.0 (*IBM SPSS Statistics for Windows*, 2013). Cox proportional hazards regression was conducted to examine the association between wellbeing scores and incidence of diabetes, heart attack, stroke, cancer, chronic lung disease and arthritis respectively. On the basis of Schoenfeld residuals, there was no evidence that the proportional hazards assumption was violated in any of these models (all p values>0.2). Survival time in days was calculated from the date of the wave 1 interview to the date of diagnosis with the disease of interest or the date of the last follow up interview, whichever occurred first. Participants diagnosed with the disease of interest at wave 1 were excluded from the analysis. Eight adjustment models were used. Model 1 adjusted for age and sex. To assess the extent to which each covariate attenuated the association between wellbeing score and disease incidence (after adjusting for age and sex), a further five models were run. Each model was adjusted for age, sex and one additional covariate: model 2 additionally adjusted for health behaviour (smoking status, alcohol consumption and physical activity), model 3 adjusted for BMI, model 4 adjusted for CES-D score, model 5 adjusted for wealth and education and model 6 adjusted for relationship status. Model 7 adjusted for prevalent co-morbidities (present at wave 1) which increase the risk of specific disease outcomes and may be associated with lower wellbeing. For the outcome of diabetes, model 7 adjusted for reported

hypertension; for heart attack and stroke, model 7 adjusted for reported diabetes and hypertension; for the outcome of chronic lung disease, model 7 adjusted for reported asthma. To assess the association between wellbeing scores and disease incidence after adjusting for all the covariates, a final adjustment model was run, this model included all covariates i.e. age, sex, smoking status, alcohol consumption, physical activity, BMI, CES-D, wealth, education, relationship status and relevant comorbidities. Hazard ratios (HR) and 95% confidence intervals (CI) for each chronic disease are expressed according to a standard deviation (SD) increase in wellbeing score.

Additional analysis

We tested whether associations between wellbeing and risk of incident disease varied according to gender and age by including multiplicative interaction terms in the fully adjusted models for each disease outcome (e.g. wellbeing × age). To explore which aspects of wellbeing were associated with risk of chronic disease, further Cox regression analysis was conducted using the wellbeing subdomains of control, autonomy, self-realisation and pleasure.

Levels of wellbeing may vary over time; thus, employing the baseline measure of wellbeing in the Cox regression analysis may result in an underestimation of the association between wellbeing and disease incidence. To account for variation in wellbeing (or other covariates) over the follow-up period, the analysis was repeated using time-varying wellbeing as well as CES-D, BMI, relationship status, alcohol consumption, smoking status, and physical activity. Baseline measures were employed for the remaining covariates (age, sex, education and wealth) – it was assumed that these variables would remain stable over the follow up period. Apart from BMI, data for these variables were collected at each wave, data for BMI was collected at every alternative wave (0, 2 and 4) during an interview with a nurse. Time-dependent covariates were created for the relevant variables using all available data from waves 1-4, such that the value used in the Cox regression varied with time.

To reduce the risk of reverse causality (undiagnosed pre-existing disease influencing wellbeing), for outcomes that remained significantly associated with wellbeing scores in the fully adjusted model, the regression was repeated excluding incident cases in the first two years of follow up.

Table 2.1

Baseline characteristics stratified according to tertiles of wellbeing score (lowest, middle, and highest subjective wellbeing); n = 8,182

Characteristics	**Lowest**	**Middle**	**Highest**	***p*-trend**[a]
Age (yrs.), *M* (SD)	64 (11)	64 (11)	62 (10)	<0.001
CES-D score, *Mdn* (IQR)	2 (1-4)	1 (0-2)	0 (0-1)	<0.001
Wealth, *M* (SD) (in £100,000)	1.56 (3.74)	2.12 (2.80)	3.10 (5.34)	<0.001
BMI, ($kg/m^{2)}$ *M* (SD)	28.08 (4.93)	27.56 (4.38)	27.05 (4.20)	<0.001
Female, No. (%)	1486 (55)	1492 (55)	1606 (58)	0.01
Physical activity, No. (%)				<0.001
Physically inactive	347 (13)	143 (5)	90 (3)	
Mild physical activity	568 (21)	348 (13)	177 (6)	
Moderate physical activity	1290 (47)	1358 (50)	1378 (50)	
Vigorous physical activity	522 (19)	849 (32)	1112 (40)	
Alcohol consumption, No (%)				<0.001
At least twice a day	99 (4)	121 (5)	122 (4)	
Daily or almost daily	549 (20)	662 (25)	811 (29)	
Once or twice a week	766 (28)	910 (34)	942 (34)	
Once or twice a month	290 (11)	299 (11)	308 (11)	
Special occasions only	635 (23)	477 (18)	394 (14)	
Not at all	388 (14)	229 (9)	180 (7)	
Smoking status, No. (%)				<0.001

Smoker	612 (22)	427 (16)	374 (14)	
Former smoker	1248 (46)	1242 (46)	1263 (45)	
Non-smoker	867 (32)	1029 (38)	1120 (41)	
No partner, No. (%)	941 (35)	719 (27)	578 (21)	<0.001
Education, No. (%)				<0.001
Less than O-level	216 (8)	323 (12)	483 (16)	
O-level	255 (9)	338 (13)	402 (15)	
A-level	176 (7)	181 (7)	206 (8)	
Higher below degree	439 (16)	499 (19)	520 (19)	
Degree level	1641 (60)	1357 (50)	1146 (42)	
History of arthritis, No. (%)	1175 (43)	809 (30)	530 (19)	<0.001
History of cancer, No. (%)	169 (6)	148 (6)	137 (5)	0.14
History of diabetes, No. (%)	239 (9)	168 (6)	102 (4)	<0.001
History of heart attack, No. (%)	195 (7)	123 (5)	90 (3)	<0.001
History of stroke, No. (%)	155 (6)	72 (3)	49 (2)	<0.001
History of lung disease, No. (%)	261 (10)	121 (5)	87 (3)	<0.001
History of asthma, No. (%)	398 (15)	302 (11)	231 (8)	<0.001
History of hypertension, No. (%)	1108 (41)	1018 (38)	841 (31)	<0.001

[a]statistical significance is based $\chi 2$ tests or one-way ANOVA, as appropriate.

Results

Sample characteristics

Table 2.1 shows the baseline characteristics of the sample (n = 8,182) according to tertiles of wellbeing. On average, people with higher wellbeing were younger, had

lower CES-D scores, were wealthier, had lower BMI, were more physically active, consumed more alcohol and had a higher level of education than people reporting low levels of wellbeing. People with higher wellbeing were also more likely to be female, in a relationship, not to smoke, and less likely to report a history of arthritis, diabetes, heart attack, hypertension, chronic lung disease, and stroke.

Preliminary analysis

Preliminary analysis indicated that the association between wellbeing score and chronic disease incidence did not differ according to sex (*p* for interaction terms all >0.05). However, we found that the strength of association between wellbeing score and incidence of diabetes, heart attack and chronic lung disease did differ significantly by age. Consequently, in the case of these three disease outcomes, separate Cox proportional hazards regression analysis was conducted for three age groups (under 60, 60-69 and 70 and over).

Cox proportional hazards regression

Tables 2.2-2.7 display HRs for incident arthritis, cancer, stroke, diabetes, heart attack and chronic lung disease according to a SD increase in overall wellbeing score. HRs are adjusted for age and sex (model 1), followed by additional adjustment for health behaviours (model 2), BMI (model 3), CES-D score (model 4), total household wealth education (model 5) and relationship status (model 6) or relevant comorbidities (model 7).

Arthritis risk

936 participants reported a new diagnosis of arthritis during follow-up (table 2.2). Participants with higher wellbeing scores had a significantly lower risk of incident arthritis after adjustment for age and sex. A SD increase in wellbeing score was associated with a 16% reduction in risk. This relationship remained significant (although attenuated) in the fully adjusted model. The association was predominantly attenuated by adjusting for CES-D score (25% attenuation). In the fully adjusted model, a SD increase in wellbeing score was associated with an 11% (HR: 0.89; 95% CI: 0.83-0.96) decrease in arthritis risk.

Table 2.2

Hazard ratios (95% confidence intervals) for incident arthritis according to a SD increase in wellbeing score; n = 5,374

Covariates	**HR (95% CI)**	**% Attenuation**
Age + sex	0.84 (0.78 -0.89)**	-
Age + sex + health behaviours	0.84 (0.79-0.90)**	0%
Age + sex + BMI	0.84 (0.79-0.90)**	0%
Age + sex + CES-D	0.88 (0.82-0.95)*	25%
Age + sex + wealth + education	0.85 (0.80-0.91)**	6%
Age + sex + relationship	0.84 (0.78-0.89)**	0%
All covariates	0.89 (0.83-0.96)*	31%

** $p < 0.001$

* $p < 0.05$

Cancer risk

395 new case of cancer were reported (table 2.3). No significant association was found between wellbeing and incidence of cancer.

Table 2.3

Hazard ratios (95% confidence intervals) for incident cancer according to a SD increase in wellbeing score, n = 7,474

Covariates	**HR (95% CI)**	**% Attenuation**
Age + sex	1.01 (0.91-1.13)	-
Age + sex + health behaviours	1.01 (0.90-1.12)	-
Age + sex + BMI	1.02 (0.92-1.14)	-
Age + sex + CES-D	1.08 (0.95-1.22)	-
Age + sex + wealth + education	0.99 (0.88-01.10)	-
Age + sex + relationship	1.01 (0.91-1.11)	-
All covariates	1.05 (0.92-1.20)	-

** p <0.001

* p <0.05

Stroke risk

258 new cases of stroke were reported (table 2.4). An association between wellbeing scores and incidence of stroke was observed in the age- and sex-adjusted model with 1 SD increase in wellbeing score leading to a 16% (HR: 0.84; 95% CI: 0.75-0.95) decrease in stroke risk. This association was no longer significant in the fully

adjusted model (adjusted for health behaviours, BMI, CES-D score, household wealth, education, relationship status and baseline prevalence of diabetes and hypertension). The association was predominantly attenuated by adjusting for health behaviours (44% attenuation) and wealth and education (38% attenuation).

Table 2.4

Hazard ratios (95% confidence intervals) for incident stroke according to a SD increase in wellbeing score, n = 7,738

Covariates	**HR (95% CI)**	**% Attenuation**
Age + sex	0.84 (0.75-0.95)*	-
Age + sex + health behaviours	0.91 (0.79-1.03)	44%
Age + sex + BMI	0.84 (0.74-0.95)*	0%
Age + sex + CES-D	0.84 (0.73-0.98)*	0%
Age + sex + wealth + education	0.90 (0.79-1.02)	38%
Age + sex + relationship	0.83 (0.73-0.94)*	-6%
Age + sex + hypertension + diabetes	0.86 (0.76-0.97)*	13%
All covariates	0.94 (0.81-1.09)	69%

** $p < 0.001$

* $p < 0.05$

Table 2.5

Hazard ratios (95% confidence intervals) for incident diabetes according to a SD increase in wellbeing score, n = 7,497

Covariates	**Age group[a]**	**HR (95% CI)**	**% Attenuation**
Sex	<60	0.67 (0.59-0.77)**	-
	60-69	0.79 (0.67-0.92)*	-
	70+	0.86 (0.72-1.04	-
Sex + health behaviours	<60	0.76 (0.66-0.88)**	27%
	60-69	0.89 (0.75-1.06)	48%
	70+	0.94 (0.77-1.14)	-
Sex + BMI	<60	0.69 (0.60-0.79)**	6%
	60-69	0.84 (0.72-0.99)*	24%
	70+	0.90 (0.75-1.09)	-
Sex + CES-D	<60	0.70 (0.59-0.83)**	9%
	60-69	0.83 (0.69-0.99)*	19%
	70+	0.88 (0.71-1.09)	-
Sex + wealth + education	<60	0.74 (0.64-0.85)**	21%
	60-69	0.87 (0.7-1.025)	38%
	70+	0.91 (0.76-1.10)	-
Sex + relationship	<60	0.69 (0.60-.79)**	6%
	60-69	0.80 (0.68-0.94)*	4%
	70+	0.86 (0.712-1.04)	-
Sex + hypertension	<60	0.71 (0.62-0.81)**	12%
	60-69	0.81 (0.69-0.95)*	9%

	70+	0.88 (0.73-1.06)	-
All covariates	<60	0.82 (0.68-0.98)*	45%
	60-69	0.93 (0.76-1.14)	67%
	70+	0.98 (0.77-1.24)	-

[a] Number of incident cases in each age group: <60 = 175, 60-69 = 155, 70+ = 121

** p <0.001

* p <0.05

Diabetes risk

451 new cases of diabetes were reported during follow-up (table 2.5). In preliminary analysis, we observed a significant interaction between age and wellbeing score in predicting incident diabetes. Analysis stratified by age group indicated a trend for a stronger association between wellbeing score and incident diabetes at a younger age. For the under 60 and the 60-69 age groups a significant inverse association between wellbeing score and diabetes risk was observed for model 1 (sex-adjusted). A SD increase in wellbeing score was associated with a 33% (HR: 0.67; 95% CI: 0.59-0.77) decrease in diabetes risk in the under 60 age group and a 21% decrease (HR: 0.79; 95% CI: 0.67-0.92) in the 60-69 age group. This association remained significant although attenuated in the fully adjusted model in the under 60 age group, a SD increase in wellbeing score was associated with an 18% (HR: 0.82; 95% CI: 0.68-0.98) decrease in diabetes risk. This association was predominantly attenuated by adjusting for health behaviours (27% for the under 60 age group and 48% for the 60-69 age group) and SES (21% for the under 60 age group and 38% for the 60-69 age group). No significant association was observed in the 70 and over age group.

Table 2.6

Hazard ratios (95% confidence intervals) for incident heart attack according to a SD increase in wellbeing score, n = 7,615

Covariates	**Age group[a]**	**HR (95% CI)**	**% Attenuation**
Sex	<60	0.63 (0.48-0.83)*	-
	60-69	0.68 (0.54-0.87)*	-
	70+	0.89 (0.71-1.12)	-
Sex + health behaviours	<60	0.75 (0.55-1.01)	32%
	60-69	0.73 (0.56-0.95)*	16%
	70+	0.97 (0.76-1.23)	-
Sex + BMI	<60	0.64 (0.49-0.84)*	3%
	60-69	0.70 (0.55-0.89)*	6%
	70+	0.897 (0.71-1.12)	-
Sex + CES-D	<60	0.67 (0.47-0.95)*	11%
	60-69	0.73 (0.54-0.97)*	16%
	70+	0.88 (0.68-1.15)	-
Sex + wealth + education	<60	0.68 (0.51-0.92)*	14%
	60-69	0.70 (0.54-0.92)*	6%
	70+	0.91 (0.72-1.14)	-
Sex + relationship	<60	0.64(0.48-0.84)*	3%
	60-69	0.66(0.52-0.85)*	-12%
	70+	0.90 (0.72-1.13)	-
Sex + diabetes + hypertension	<60	0.68 (0.52-0.89)*	14%

	60-69	0.68 (0.53-0.86)*	0%
	70+	0.91 (0.72-1.14)	-
All covariates	<60	0.80 (0.54-1.17)	46%
	60-69	0.78 (0.56-1.07)	31%
	70+	0.95 (0.72-1.25)	-

[a] Number of incident cases in each age group: <60 = 42, 60-69 = 54, 70+ = 89

** p <0.001

* p <0.05

Heart attack risk

185 new cases of heart attack were reported (table 2.6). In preliminary analysis predicting heart attack risk, there was a significant interaction between age and wellbeing score. Analysis stratified by age group indicated a trend for a stronger association between wellbeing scores and incident heart attack at a younger age. A significant inverse association between wellbeing scores and heart attack risk was observed for the under 60 and 60-69 age groups, but not for those aged 70 or over. As SD increase in wellbeing score was associated with a 37% (HR: 0.63; 95% CI: 0.48-0.83) decrease in heart attack risk for the under 60 age group, and a 32% (HR: 0.68, 0.54-0.87) decrease in risk for the 60-69 age group. This association was no longer significant in the fully adjusted model. The association between wellbeing score and heart attack risk was most strongly attenuated by adjusting for health behaviours (32% attenuation in the under 60 age group and 16% attenuation in the 60-69 age group) and depression (11% attenuation in the under 60 group and 16% in the 60-69 age group).

Chronic lung disease risk

302 new cases of chronic lung disease were reported (table 2.7). In preliminary analysis, we observed a significant interaction between age and wellbeing score in predicting incident chronic lung disease. Again, analysis stratified by age indicated a trend for a stronger association between wellbeing score and incident lung disease at younger ages. In the sex-adjusted model, the association between wellbeing score and chronic lung disease risk was significant for all 3 age groups. A SD increase in wellbeing score was associated with a 43% (0.57; 0.48-0.67) decrease in chronic lung disease risk in the under 60 age group, a 36% (HR: 0.64; 95% CI: 0.54-0.76) decrease in risk in the 60-69 age group and a 25% (HR: 0.75; 95% CI: 0.61-0.93) decrease in risk in the 70+ age group. This association remained significant in the fully adjusted model for the under 60 age group, a SD increase in wellbeing score was associated with a 23% (HR: 0.77; 95% CI: 0.61-0.97) decrease in chronic lung disease risk. The association between wellbeing score and chronic lung disease risk was most strongly attenuated by adjusting for health behaviours, (19% for the under 60 age group, 25% for the 60-69 age group and 24% for the 70+ group) CES-D score (16% for the under 60 age group, 28% for the 60-69 age group and 8% for the 70+ group) and wealth and education (19% for the under 60 age group, 28% for the 60-69 age group and 16% for the 70+ group).

Table 2.7

Hazard ratios (95% confidence intervals) for incident chronic lung disease according to a SD increase in wellbeing score, n = 7,577

Covariates	**Age group[a]**	**HR (95% CI)**	**% Attenuation**
Sex	<60	0.57 (0.48-0.67)**	-
	60-69	0.64 (0.54-0.76)**	-
	70+	0.75 (0.61-0.93)*	-
Sex + health behaviours	<60	0.65 (0.55-0.78)**	19%
	60-69	0.73 (0.61-0.89)*	25%
	70+	0.81 (0.65-1.01)	24%
Sex + BMI	<60	0.56 (0.48-0.66)**	-2%
	60-69	0.62 (0.52-0.74)**	-5%
	70+	0.76 (0.61-0.93)*	4%
Sex + CES-D	<60	0.64 (0.52-0.80)**	16%
	60-69	0.74 (0.60-0.92)*	28%
	70+	(0.77 (0.60-0.98)*	8%
Sex + wealth + education	<60	0.65 (0.54-0.77)**	19%
	60-69	0.74 (0.61-0.89)*	28%
	70+	0.79 (0.64-0.98)*	16%
Sex + relationship	<60	0.60 (0.50-00.70)**	7%
	60-69	(0.65 (0.54-0.77)**	3%
	70+	0.76 (0.62-0.93)*	4%

Sex + history of asthma	<60	0.60 (0.50-0.70)**	6.98%
	60-69	0.67 (0.57-0.80)**	8%
	70+	0.77 (0.63-0.95)*	0%
All covariates	<60	0.77 (0.61-0.97)*	47%
	60-69	0.88 (0.70-1.11)	67%
	70+	0.84 (0.65-1.08)	36%

[a] Number of incident cases in each age group: <60 = 107, 60-69 = 103, 70+ = 92

** p <0.001

* p <0.05

Subdomains of the CASP-19

Analysis with the 4 subdomains of CASP-19 (control, autonomy, self-realisation and pleasure), revealed a significant association with disease risk after adjusting for traditional risk factor in the case of arthritis, heart attack (in the under 60 age group) and chronic lung disease (in all 3 age groups) (see table 2.8). Self-realisation emerged as a significant predictor of all three disease outcomes. Autonomy was associated with arthritis and chronic lung disease risk. Control was associated with heart attack risk. To test for the effect of missing data, for those with one missing subdomain item we imputed a score for the missing item based on their mean score for the complete items in that subdomain. The Cox regression for the association between disease risk and wellbeing subdomains was then repeated including participants with imputed values. The results obtained were very similar to the results for participants with complete data. Only results from these latter analysis are presented here (table 2.8).

Analysis with CASP-19 subdomains involved 48 significance tests, this increased the chance of a false positive result. Consequently, we corrected the p-values from this analysis for multiple comparisons using Hochberg's False Discovery Rate (FDR) correction (Benjamini & Hochberg, 1995). All the significant age- and sex-adjusted associations reported in table 2.8 survived FDR correction, apart from the association between self-realisation and chronic lung disease risk in the 70 and over age group (p = 0.052). Of the significant fully adjusted associations reported in table 2.8, only the association between self-realisation and arthritis risk survived FDR correction (p = 0.036).

Table 2.8

Hazard ratios (95% confidence intervals) for incident arthritis, cancer, stroke, diabetes, heart attack and chronic lung disease according to a SD increase in control, autonomy, self-realisation, or pleasure

Chronic disease	**subdomain**	**Model 1 HR (95%-CI)**	**Model 2 HR (95%-CI)**
Arthritis	Control	0.88 (0.82-0.94)**	0.95 (0.87-1.03)
	Autonomy	0.86 (0.80-0.92)**	0.92 (0.85-0.99)*
	Self-realisation	0.82 (0.76-0.88)**	0.87 (0.80-0.94)**
	Pleasure	0.91 (0.85-0.96)*	0.95 (0.90-1.02)
Cancer	Autonomy	0.99 (0.89-1.10)	1.01 (0.90-1.14)
	Control	0.95 (0.85-1.05)	0.96 (0.85-1.09)
	Self-realisation	1.02 (0.91-1.14)	1.05 (0.92-1.19)
	Pleasure	0.99 (0.90-1.10)	1.00 (0.90-1.13)
Stroke	Autonomy	0.78 (0.68-0.88)**	0.89 (0.77-1.02)
	Control	0.83 (0.73-.94)*	0.95 (0.82-1.09)
	Self-realisation	0.84 (0.74-0.95)*	0.96 (0.83-1.12)
	Pleasure	0.99 (0.87-1.13)	1.07 (0.92-1.24)
Diabetes < 60	Autonomy	0.68 (0.59-0.79)**	0.86 (0.72-1.02)
	Control	0.71 (0.60-0.83)**	0.92 (0.76-1.12)
	Self-realisation	0.67 (0.57-0.77)**	0.85 (0.70-1.04)
	Pleasure	0.78 (0.69-0.89)**	0.88 (0.75-1.02)
Diabetes 60-69	Autonomy	0.73 (0.62-0.85)**	0.85 (0.71-1.02)
	Control	0.71 (0.60-0.84)**	0.85 (0.70-1.03)
	Self-realisation	0.76 (0.65-0.89)*	0.91 (0.74-1.11)

	Pleasure	0.96 (0.82-1.14)	1.05 (0.87-1.27)
Diabetes 70+	Autonomy	0.86 (0.72-1.03)	0.99 (0.81-1.21)
	Control	0.85 (0.72-1.01)	0.97 (0.79-1.19)
	Self-realisation	0.91 (0.77-1.08)	1.03 (0.84-1.27)
	Pleasure	0.91 (0.76-1.08)	0.95 (0.78-1.16)
Heart attack < 60	Autonomy	0.69 (0.51-.93)*	0.89 (0.62-1.26)
	Control	0.56 (0.43-0.74)**	0.67 (0.48-0.93)*
	Self-realisation	0.62 (0.47-0.81)**	0.77 (0.54-1.12)
	Pleasure	0.82 (0.63-1.07)	1.01 (0.72-1.41)
Heart attack 60-69	Autonomy	0.69 (0.53-0.89)*	0.80 (0.5-1.08)
	Control	0.77 (0.60-0.99)	0.91- (0.67-1.22)
	Self-realisation	0.68 (0.53-0.86)**	0.73 (0.55-.98)*
	Pleasure	0.87 (0.69-1.11)	0.97 (0.72-1.29)
Heart attack 70+	Autonomy	0.87 (0.70-1.08)	0.89 (0.70-1.13)
	Control	0.81 (0.65-0.99)*	0.84 (0.65-1.08)
	Self-realisation	0.92 (0.74-1.15)	0.97 (0.75-1.25)
	Pleasure	0.73 (0.65-0.82)	0.89 (0.76-1.04)
Lung disease<60	Autonomy	0.63 (0.52-0.77)**	0.79 (0.63-0.99)*
	Control	0.60 (0.49.74)**	0.80 (0.63-1.02)
	Self-realisation	0.54 (0.45-0.66)**	0.69 (0.54-0.89)*
	Pleasure	0.69 (0.60-0.79)**	0.83 (0.69-1.00)
Lung disease 60-69	Autonomy	0.68 (0.56 -0.81)**	0.93 (0.76-1.16)
	Control	0.61 (0.50 - 0.73)**	0.82 (0.65-1.02)
	Self-realisation	0.59 (0.50-0.70)**	0.79 (0.63 -0.99)*
	Pleasure	0.83 (0.71-0.96)*	0.99 (0.81-1.21)

Lung disease 70+	Autonomy	0.74 (0.60 -0.91)*	0.77 (0.61-0.97)*
	Control	0.75 (0.61-0.91)*	0.80 (0.64-1.01)
	Self-realisation	0.81 (0.66-0.98)*	0.91 (0.72-1.15)
	Pleasure	1.00 (0.78-1.27)	1.15 (0.87-1.51)

Model 1: Adjusted for age and sex.

Model 2: Further adjusted for smoking, alcohol intake, physical activity, total net wealth, CES-D score, education, relationship status and relevant comorbidities.

** p <0.001

* p <0.05

Analysis with time-varying covariates

Estimates of the association between wellbeing score and risk of incident disease obtained when wellbeing and selected covariates were treated as time-varying were in general very similar to those obtained when a single baseline measure of these variables was used (see table 2.9 for a comparison of results).

Analysis including only core participants

At wave 1, the ELSA sample consisted of 11,390 core members, who were selected at random from the community, and 708 partners of those core members. To test whether including partners in our sample affected our results, we re-ran our analysis including only core members of the ELSA sample. Estimates of the association between wellbeing and disease risk were mostly unchanged by the exclusion of partners. However, the association between wellbeing and risk of diabetes in the

under 60 age group was non-significant (HR: 0.82, 95% CI: 0.66-1.02), following adjustments for covariate variables.

Analysis with fewer age groups

The number of incident cases of heart attack in each age group was low, there were 42, 54 and 89 incident cases in the <60, 60-69 and 70+ age groups respectively. To increase power, we re-ran analysis predicting heart attack risk dividing the sample into two age groups: <65 and ≥65. Following adjustment for covariate variables, the association between wellbeing and heart attack risk was non-significant in both age groups. Fully-adjusted estimates were HR: 0.84 (95% CI: 0.63-1.12) for the <65 age group, and HR: 0.86 (0.69-1.06) for the ≥65 age group.

Sensitivity analysis

We tested whether exclusion of participants with missing covariate data had biased the results. For each disease outcome, the age- and sex-adjusted model was re-run including participants with missing covariate data. The results were very similar to those obtained in the sample with complete data indicating that the exclusion of participants with missing covariate data did not significantly affect the results (see table 2.10). We also tested for bias due to the exclusion of participants with missing wellbeing data. In an age- and sex-adjusted model, missing wellbeing data did not predict incident arthritis, stroke, diabetes or heart attack, however, participants with missing wellbeing data were significantly more likely to develop chronic lung disease and were less likely to be diagnosed with cancer.

Table 2.9

Hazard ratios (95% confidence intervals) for incident arthritis, cancer, stroke, diabetes, heart attack and chronic lung disease according to a SD increase in wellbeing score from analysis with baseline covariates and from analysis with time dependent covariates. Analysis predicting diabetes, heart attack and chronic lung disease were stratified by age.

Chronic disease	**Covariates**	**Model 1 HR (95%-CI)**	**Model 2 HR (95%-CI)**
Arthritis	Baseline	0.84 (0.78-0.89)**	0.89 (0.83-0.96)*
	Time dependent	0.82 (0.76-0.89)*	0.90 (0.82-0.99)*
Cancer	Baseline	1.01 (0.91-1.13)	1.05 (0.92-1.20)
	Time dependent	1.02 (0 .90-1.15)	1.05 (0.91-1.22)
Stroke	Baseline	0.84 (0.75-0.95)*	0.94 (0.81-1.09)
	Time dependent	0.84 (0.72-0.99)*	0.89 (0.73-1.09)
Diabetes < 60	Baseline	0.67 (0.59-0.77)**	0.82 (0.68-0.98)*
	Time dependent	0.69 (0.59-0.80)**	0.85 (0.69-1.03)
Diabetes 60-69	Baseline	0.79 (0.67-0.92)*	0.93 (0.76-1.14)
	Time dependent	0.75 (0.63-90)*	91 (0.73-1.14)
Diabetes 70+	Baseline	0.86 (0.72-1.04)	0.98 (0.77-1.24)
	Time dependent	0.72 (0.64-80)*	0.89 (0.71-1.03)
Heart attack < 60	Baseline	0.63 (0.48-0.83)*	0.80 (0.54-1.17)
	Time dependent	0.60 (0.41-0.82)*	0.63 (0.39-1.02)
Heart attack 60-69	Baseline	0.68 (0.54-0.87)*	0.78 (0.56-1.07)
	Time dependent	0.73 (0.54-0.96)*	0.80 (0.55-1.56)
Heart attack 70+	Baseline	0.89 (0.71-1.12)	0.95 (0.72-1.25)
	Time dependent	0.87 (0.67-1.34)	0.96 (0.69-1.34)

Lung disease <60	Baseline	0.57 (0.48-0.67)**	0.77 (0.61-0.97)*
	Time dependent	0.60 (0.50-0.72)**	0.70 (0.55-0.90)*
Lung disease 60-69	Baseline	0.64 (0.54-0.76)**	0.88 (0.70-1.11)
	Time dependent	0.64 (0.52-0.78)**	0.90 (0.69-1.18)
Lung disease 70+	Baseline	0.75 (0.61-0.93)**	0.84 (0.65-1.08)
	Time dependent	0.76 (0.58-0.99)*	0.83 (0.59-1.16)

Model 1: Adjusted for age and sex.

Model 2: Further adjusted for smoking, alcohol intake, physical activity, total net wealth, CES-D score, education, relationship status and relevant comorbidities.

** p <0.001

* p <0.05

Analysis excluding health related items from the CASP-19

The measure of wellbeing (the CASP-19) includes items explicitly related to health: 'my health stops me from doing the things I want to do' (Vanhoutte, 2012). We excluded this item from the wellbeing measure and re-ran the fully adjusted analysis for each disease outcome, replacing the complete wellbeing score with this modified version. On average, HRs from the analysis with the modified wellbeing score were higher by 0.02-0.03 than the HRs from the original analysis (including responses to all CASP-19 questions).

Table 2.10

Age- and sex-adjusted hazard ratios (95% confidence intervals) for incident arthritis, cancer, stroke, diabetes, heart attack and chronic lung disease according to a SD increase in wellbeing score from analysis excluding participants with missing covariate data and from analysis including participants with missing covariate data. Analysis predicting diabetes, heart attack and chronic lung disease was stratified by age.

Chronic disease	**Participants included/excluded**	**Model 1 HR (95%-CI)**
Arthritis	Included	0.84 (0.79-0.90)**
	Excluded	0.84 (0.78-0.89)**
Cancer	Included	1.02 (0.92-1.13)
	Excluded	1.01 (0.91-1.13)
Stroke	Included	0.80 (0.72-0.90)*
	Excluded	0.84 (0.75-0.95)*
Diabetes (<60)	Included	0.66 (0.58-0.74)**
	Excluded	0.67 (0.59-0.77)**
Diabetes (60-69)	Included	0.79 (0.68-0.92)*
	Excluded	0.79 (0.67-0.92)*
Diabetes (70+)	Included	0.86 (0.72-1.01)
	Excluded	0.86 (0.72-1.04)
Heart attack (<60)	Included	0.64 (0.50-0.81)*
	Excluded	0.63 (0.48-0.83)*
Heart attack (60-69)	Included	0.71 (0.56-0.90)*
	Excluded	0.68 (0.54-0.87)*
Heart attack (70+)	Included	0.96 (0.78-1.18)

	Excluded	0.89 (0.71-1.12)
Lung disease (<60)	Included	0.56 (0.48-0.66)**
	Excluded	0.57 (0.48-0.67)**
Lung disease (60-69)	Included	0.66 (0.56-0.78)**
	Excluded	0.64 (0.54-0.76)**
Lung disease (70+)	Included	0.71 (0.59-0.86)**
	Excluded	0.75 (0.61-0.93)*

Model 1: Adjusted for age and sex, or only sex for outcomes stratified by age

** p <0.001

* p <0.05

Analysis excluding incident cases in the first two years of follow up

For the three chronic conditions that were significantly associated with wellbeing in the fully adjusted model: arthritis, diabetes (for those aged <60) and chronic lung disease (for those aged <60), we repeated the analysis excluding cases diagnosed in the first 2 years of follow-up. The association between wellbeing and risk of arthritis was only slightly changed, suggesting that the association is unlikely to reflect reverse causation whereby undiagnosed disease at baseline affected well-being. However, the association between well-being and diabetes or chronic lung disease incidence was no longer significant. The fully adjusted HRs for arthritis, diabetes, and chronic lung disease were 0.86 (95% CI: 0.78-0.95), 0.82 (95% CI = 0.66–1.00), and 0.80 (95% CI = 0.60-1.05) respectively. 353 cases of arthritis, 62 cases of diabetes, and 53 cases of chronic lung disease were excluded from this sensitivity analysis.

The estimate from analysis excluding cases diagnosed in the first two years of follow up was similar HR: 0.86 (95% CI: 0.78-0.95). This suggests that the association between wellbeing and arthritis risk is unlikely to reflect reverse causation whereby undiagnosed disease at baseline affected wellbeing.

Discussion

Summary

In this longitudinal study of people aged 50 and over, those who reported a higher level of wellbeing at baseline had a lower risk of disease incidence. However, the extent of this association differed according to type of chronic disease, sub-domain of wellbeing and in some cases age group. The association between wellbeing and risk of arthritis, diabetes and chronic lung disease remained significant following adjustment for established risk factors and depressive symptoms. The association between wellbeing and risk of heart attack or stroke was significant following adjustment for age and sex but was not significant in the fully adjusted model. Wellbeing was not associated with cancer risk in any of our models. An age interaction was observed for diabetes, heart attack and chronic lung disease, with a stronger association between wellbeing and disease risk at younger ages.

Arthritis risk

This is the first longitudinal study to document an association between wellbeing and arthritis risk. This association remained significant after adjusting for established risk factors; however, the effect size was small. Examination of the analytical models suggests that the association between wellbeing and arthritis risk was partially cofounded by demographic variables and depressive symptoms – with depressive

symptoms accounting for a large proportion of this association. The association between wellbeing and arthritis risk was not fully explained by the potential mediating factors, health behaviours and BMI. This suggests that additional mechanisms, not controlled for in our analysis, are involved in the association between wellbeing and arthritis risk. Wellbeing is associated with physiological processes relevant to arthritis risk or symptom expression. Specifically, high wellbeing is associated with lower levels of inflammatory markers (Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008; Steptoe, Wardle, & Marmot, 2005). Thus, wellbeing might lessen the expression of arthritic symptoms by reducing the extent of inflammation. However, further work is needed to establish whether the association between wellbeing and inflammatory processes is causal, and, to identify the direction of this association. The relationship between psychological factors and the onset of arthritis has received little empirical attention (Nicassio, Draper, & Ormseth, 2013). However, one longitudinal study reported a positive association between perceived stress and onset of arthritis three years later (Harris, Loxton, Sibbritt, & Byles, 2013).

Cancer risk

We found no significant association between wellbeing and incident cancer. These findings contrast with previous reports of a significant association between wellbeing and cancer (Feller et al., 2013) and breast cancer specifically (Wakai et al., 2007). However, findings in this area are mixed. Our results are similar to those reported by Lillberg et al. (2002), who found no association between life satisfaction and breast cancer incidence. It is possible that wellbeing is associated with some types of

cancer. Previous studies indicate that psychological factors such as stress and depression specifically increase the risk of virus-related cancers (Reiche, Nunes, & Morimoto, 2004). We were unable to discriminate between different types of cancers in our analysis, and thus may have missed these specific associations.

Stroke risk

Higher wellbeing was associated with a reduced risk of incident stroke in the age- and sex-adjusted model. This association did not persist in the fully adjusted model. Some studies into wellbeing and risk of cardiovascular disease or stroke, reported a similar attenuation after adjusting for established risk factors (Feller et al., 2013; Richman, Kubzansky, Maselko, Ackerson, & Bauer, 2009; Shirai et al., 2009). However, others found a significant association between positive affect and incident stroke after adjusting for demographic factors, prevalent diabetes, hypertension and health behaviours (Ostir, Markides, Peek, & Goodwin, 2001). Difference in sample age (all >65) and the inclusion of fatal stroke cases could explain why this latter study found a stronger association than that found in this study

Heart attack risk

We observed a significant association between wellbeing and heart attack risk in a sex-adjusted model among participants younger than 70. However, this association was not significant in the fully adjusted model – suggesting that the association between wellbeing and heart attack risk may be fully mediated or confounded by established risk factors. Two studies reported a significant association between measures of wellbeing and incident coronary heart disease after adjusting for established risk factors (Davidson et al., 2010; Kubzansky et al., 2001); however,

neither study adjusted for the potentially confounding or mediating effect of physical activity. By contrast, Feller et al. (2013) found no significant association between life satisfaction and incident heart attack in a minimally adjusted model (stratified by age and study center) or in a model adjusted for established risk factors.

Diabetes risk

In the sex-adjusted model, wellbeing was significantly associated with diabetes risk in the under 60 and the 60-69 age groups. This association remained significant although attenuated in the fully adjusted model for the under 60 age group but not the 60-69 age group. No association was found for the 70+ age group. A previous study documented an association between wellbeing (emotional vitality and life satisfaction) and physician-diagnosed diabetes (Boehm, Trudel-Fitzgerald, Kivimaki, & Kubzansky, 2015). In line with our results, this association remained significant after adjusting for demographic variables, health behaviours, BMI, and depressive symptoms. However, a second study into the association between life satisfaction and diabetes risk documented a weaker association (Feller et al., 2013). In this latter study, life satisfaction was only associated with diabetes risk in women, and this association was not significant after excluding incident diabetes in the first 2 years of follow up. Other psychosocial factors not controlled for in the current study including stress, hostility and anxiety are associated with risk of type 2 diabetes (Engum, 2007; Heraclides, Chandola, Witte, & Brunner, 2009; Pouwer, Kupper, & Adriaanse, 2010; Shen, Countryman, Spiro, & Niaura, 2008). Feller et al. (2013) suggest that wellbeing may provide a buffer against the influence of these risk factors. Alternatively, wellbeing could impact diabetes risk via its association with

lower levels of C-reactive protein (CRP) (Stellar et al., 2015). Elevated CRP is an established predictor of type 2 diabetes risk (Hu, Meigs, Li, Rifai, & Manson, 2004). However, the association between wellbeing and CRP has only been documented in cross-sectional research (Stellar et al., 2015). Therefore, the direction of association between wellbeing and this inflammatory marker is not yet clear.

Chronic lung disease risk

We observed a significant association between wellbeing and chronic lung disease risk in all three age groups in the sex adjusted model. However, this association was only significant for the under 60 age group following adjustment for depressive symptoms and established risk factors. This is the first study to document a significant association between wellbeing and chronic lung disease incidence. Chronic inflammation is central to the pathophysiology of chronic lung diseases (Yamamoto et al., 1997); thus, similarly to the case of arthritis or diabetes, wellbeing may be linked to chronic lung disease risk via its association with inflammatory processes (Stellar et al., 2015; Steptoe, O'Donnell, Badrick, Kumari, & Marmot, 2008).

Underlying mechanisms

Our findings suggest that the strength of association between wellbeing and disease risk could be disease-dependent. Wellbeing was most strongly associated with risk of arthritis, diabetes and chronic lung disease. One possible explanation for this finding is that wellbeing is related to processes specifically relevant to the aetiology of these chronic diseases. For instance, elevated levels of inflammatory markers are associated with lower wellbeing (Dockray & Steptoe, 2010) and the development of

type 2 diabetes (Hu et al., 2004), chronic lung disease (Yamamoto et al., 1997) and arthritis (Sokolove & Lepus, 2013). It should also be noted that the effect of reverse causality (undiagnosed disease symptoms impacting wellbeing) may be most apparent in the case of diseases such as arthritis, diabetes or chronic lung disease because clinical diagnosis of these diseases often occurs some time after disease onset. We attempted to control for this effect by excluding incident cases in the first two years of follow up in our analysis. The association between wellbeing and diabetes or chronic lung disease was no longer significant following this exclusion – suggesting that reverse causality may play a role. The chronic diseases that were robustly associated with wellbeing were also the most common. Our study may have been underpowered to detect associations between wellbeing and less common conditions such as heart attack and stroke as there were fewer incident cases of these conditions (185 and 258 respectively). Finally, compared with arthritis, diabetes and chronic lung disease, heart attack and stroke are more likely to be fatal in the short term. We did not include fatal incidence of heart attack or stroke in our analysis, and therefore, may have underestimated the association between wellbeing and the risk of these chronic conditions as a result.

Although our results could support the idea that wellbeing is differentially related to different diseases, no previous studies documented this pattern of specificity. Feller et al. (2013) who included a number of the same disease outcomes as our study (diabetes, cancer, stroke and myocardial infarction), found a different pattern of association, the strongest association between life satisfaction and disease risk was observed for cancer and stroke.

Adjustment for each covariate separately allowed for a closer examination of which covariates potentially mediated or confounded the association between wellbeing and disease risk. Firstly, as expected, adjusting for depressive symptoms attenuated the association between wellbeing and disease risk. Depressive symptoms may act as a confound of this risk association as depression is negatively correlated with wellbeing and, is associated with a higher risk of chronic disease (Hemingway & Marmot, 1999; Knol et al., 2006; Russell & Carroll, 1999). However, depressive symptoms did not fully account for associations between wellbeing and disease risk; in fact, the degree of attenuation following adjustment for depressive symptoms was generally moderate ranging from 11% attenuation for heart attack risk to 25% attenuation for arthritis risk. Adjusting for relationship status had little to no effect. Although marital status is strongly related to wellbeing (H. K. Kim & McKenry, 2002), the association between marital status and disease risk is more complicated. A positive association between marital status and disease risk in men is well established (Ben-Shlomo, Smith, Shipley, & Marmot, 1993; De Leon, Apples, Otten, & Schouten, 1992); however, a number of studies failed to find a protective effect in women (Eaker, Sullivan, Kelly-Hayes, D'Agostino Sr, & Benjamin, 2007; Valkonen, 1982). In addition, marital stress is associated with an increased risk of poor health (Orth-Gomer et al., 2000). Thus, controlling for marital quality as well as status may be necessary in future studies. Adjusting for socioeconomic status (SES) moderately attenuated associations between wellbeing and disease risk. SES could confound this risk association. More advantaged SES, as indexed by wealth and education level, is associated with higher wellbeing in old age (Martin Pinquart & Sörensen, 2000) and is also associated with reduced risk of a number of chronic diseases including:

diabetes, arthritis and stroke (Dalstra et al., 2005). Controlling for history of diabetes, hypertension and asthma led to a moderate attenuation of the association between wellbeing and incident heart attack, stroke, diabetes and chronic lung disease, suggesting that comorbidity may play a role in the associations between wellbeing and risk of these diseases. A similar level of attenuation after controlling for co-morbidity was reported by Feller et al. (2013) for the outcomes of stroke, diabetes and myocardial infarction.

It is possible that health behaviours mediate the association between wellbeing and health (Pressman & Cohen, 2005). In support of this idea, we found that adjusting for health behaviours had a large attenuating effect on associations between wellbeing and disease risk. By contrast, BMI did attenuate the association between wellbeing and disease incidence in the case of diabetes, but had minimal or no effect for the remaining disease outcomes. A number of studies reported no association between wellbeing and BMI (Doll, Petersen, & Stewart-Brown, 2000; Wardle & Cooke, 2005). This lack of association could account for the small effect associated with adjusting for BMI in the current study; however, in contrast with previous reports (Doll et al., 2000; Wardle & Cooke, 2005), a significant inverse association between BMI and wellbeing scores was observed (see table 2.1). However, the magnitude of this difference was small (the mean BMI was 28 kg/m^2 among those in the lowest tertile of wellbeing score and 27 kg/m^2 in the highest tertile).

Analysis with time-varying covariates

The time-varying model produced similar estimates to the original model (which employed baseline measures of covariates). The similarity between the two models

may reflect the fact that levels of wellbeing remained relatively stable over time. The stability of wellbeing has been documented in a number of previous studies (Charles, Reynolds, & Gatz, 2001; Diener & Diener, 1996; Lucas & Gohm, 2000). In the current sample, wellbeing scores were relatively stable over the follow up period, the test re-test correlation coefficient for wellbeing scores at wave 1 and wave 5 was high: $r = 0.62$, $p < 0.001$.

Subdomains of wellbeing

The CASP-19 can be divided into hedonic (pleasure) and eudemonic (control, autonomy and self-realisation) subdomains. Following adjustment for established risk factors, hedonic wellbeing was not associated with disease risk. However, the eudemonic domains of autonomy and self-realisation were significantly associated with a reduced risk of arthritis and chronic lung disease. Control was significantly associated with a reduced risk of heart attack among participants younger than 60, and self-realisation was significantly associated with a reduced risk of heart attack among participants aged 60-69. These results suggest that different chronic diseases may be associated with different subdomains of eudemonic but not hedonic wellbeing. In relation to these results, it is worth noting that some authors have questioned the internal consistency and dimensionality of the CASP-19 (Sim, Bartlam, & Bernard, 2011; Wiggins, Netuveli, Hyde, Higgs, & Blane, 2008). Wiggins, Netuveli, Hyde, Higgs and Blane, (2008) recommend that the subdomains of control and autonomy be treated as a single subdomain. Finally, many of these associations did not survive correction for multiple comparisons. Thus, further work confirming our findings is warranted.

Age

In the case of diabetes, heart attack and chronic lung disease, we found that the association between wellbeing and disease risk was stronger at younger ages. A similar age interaction, with a stronger effect at younger ages, was reported by a study into the association between life satisfaction and mortality risk (Collins, Glei, & Goldman, 2009). According to the authors of this previous study, this age effect might be explained by the fact that life satisfaction at younger ages is associated with increased health behaviour change and maintenance, whereas life satisfaction at older ages is more strongly associated with acceptance of health circumstances and less closely linked with a healthy lifestyle. A second possibility is that individuals who were particularly susceptible to the potentially detrimental effects of low wellbeing on health did not survive to older ages. Several studies into the association between emotional vitality, optimism, life satisfaction or general wellbeing (as indexed by the CASP-19) and incident disease or frailty found no age interaction effects (Boehm et al., 2011; Feller et al., 2013; Gale, Cooper, Deary, & Aihie Sayer, 2014). However, these studies used samples with narrower age ranges than the one in our study and therefore may have been less sensitive to age-related effects. In further contrast with our findings, two systematic reviews into the association between hedonic or eudemonic measures of wellbeing and mortality risk or cardiovascular and physiological reactivity (Chida & Steptoe, 2008; Howell et al., 2007), found that these associations were in fact stronger at older ages. Neither of these reviews reported whether the moderating effect of age was consistent across hedonic and eudemonic wellbeing measures.

Study limitations

Several potential limitations should be considered. Disease incidence was assessed using a self-report measure; the validity of self-report measures varies according to disease outcome. Studies have reported high agreement between self-report and clinically derived diagnosis in the case of cardiovascular diseases, diabetes (Haapanen, Miilunpalo, Pasanen, Oja, & Vuori, 1997) and cancer (Bush, Miller, Golden, & Hale, 1989); lower levels of agreement have been found for osteoarthritis (Haapanen et al., 1997) and respiratory diseases (Heliövaara et al., 1993). Although, others have demonstrated that self-report measures provide a valid estimate of arthritis (March, Schwarz, Carfrae, & Bagge, 1998) and chronic lung disease (Straus, Alister, Sackett, & Deeks, 2002) prevalence.

The effect of potential bias due to missing data could not be ruled out as participants with missing wellbeing data were more likely to be diagnosed with chronic lung disease and less likely to be diagnosed with cancer. In addition, we were unable to differentiate between different forms of cancer; different forms of cancer vary significantly with regards to aetiology and time course and thus, may be differentially related to prior wellbeing.

Several potentially relevant covariates were not available and therefore not included in the analysis, these included: diet, sleep quality, perceived stress and anxiety. Additionally, we had no data on fatal disease incidence. These data may have been particularly relevant in the case of heart disease and stroke.

Finally, the measure of wellbeing (the CASP-19) includes items explicitly related to health: 'my health stops me from doing the things I want to do' (Vanhoutte, 2012). Self-rated health is a powerful predictor of disease incidence (Weisen, Frishman, Aronson, & Wassertheil-Smoller, 1998). Thus, it is possible that the association between wellbeing and disease risk in our study was in part explained by this health-related question. However, excluding responses to this question in the analysis led to a minimal change in HRs. In addition, subdomains other than the one containing the health-related question (autonomy) were significantly associated with disease risk.

Strengths of the study should also be noted. These included the sample, which was relatively large. We could control for a range of established risk factor as well as symptoms of depression. The available data also allowed us to run a time-varying model to take account of variation in wellbeing over the follow up period. Analysis by theoretical sub-domain of wellbeing and separate analysis across a range of disease outcomes can be considered additional strengths.

Conclusion

To conclude, this study provides further evidence of an association between wellbeing and disease incidence. In addition to corroborating previous results regarding the association between wellbeing and incidence of stroke, diabetes, and heart attack, our findings demonstrate that this association extends to other chronic conditions including arthritis and chronic lung disease. Our findings indicate that the association between wellbeing and disease incidence may vary according to disease outcome, and, that eudemonic measures of wellbeing may be more closely linked to disease risk than hedonic measures. Finally, our results provide further insight

regarding the mechanisms underlying the association between wellbeing and disease incidence. Factors including health behaviours, BMI, depression, and demographic variables seem to account for the association between wellbeing and incident heart attack and stroke. Additional factors may be implicated in the associations between wellbeing and arthritis, diabetes, and chronic lung disease.

Chapter 3: Wellbeing and Incidence of Arthritis or Chronic Lung Disease

Introduction

In chapter 2, we found that higher wellbeing was associated with a lower risk of arthritis or chronic lung disease, and that these associations were partially independent of established risk factors and depressive symptoms. The aim of the study described in this chapter, was to test whether the inverse association between wellbeing and arthritis or chronic lung disease risk could be replicated in a nationally representative sample of older adults living in Europe and Israel.

Arthritis

Arthritis is a significant cause of disability, chronic pain and reduced quality of life, particularly for older adults. The overall prevalence of arthritis in the U.S. is approximately 20% (Centers for Disease Control, 2006); however prevalence rates are closer to 50% in the middle aged and older population (Helmick et al., 2008; Parkinson, Gibson, Robinson, & Byles, 2010). As the population ages, the prevalence of arthritis is projected to increase; by 2020, it is estimated that a further 25% of the population will suffer from arthritis (Elders, 2000). Interventions designed to reduce the incidence of arthritis have traditionally adopted the strategy of reducing the prevalence of factors associated with increased risk of two of its major forms, rheumatoid arthritis (RA) and osteoarthritis (OA). Risk factors include obesity (Felson et al., 1997), joint trauma (Wilder, Hall, Barrett, & Lemrow, 2002) and possibly physical activity (Felson et al., 1997) in the case of osteoarthritis, and

smoking (Costenbader, Feskanich, Mandl, & Karlson, 2006) in the case of rheumatoid arthritis.

Chronic lung disease

Chronic lung disease is a leading cause of morbidity and mortality worldwide (Rosenberg, Kalhan, & Mannino, 2015). This progressive disease is characterised by persistent airflow limitation caused by a combination of small airways disease (obstructive bronchiolitis) and emphysema (*Global Strategy for the Diagnosis of COPD*, 2016). Established risk factors for chronic lung disease include smoking, exposure to air pollutants, chronic lung infections, older age and genetic factors (Rosenberg et al., 2015). Recent reports suggest that prevalence rates of chronic lung disease may have stabilised in some developed countries as a result of reduced smoking prevalence (Rosenberg et al., 2015). Rosenberg et al. (2015) suggest that future trends in the prevalence of chronic lung disease will be driven by factors other than smoking prevalence.

Psychosocial risk factors for arthritis or chronic lung disease

The association between wellbeing and risk of arthritis or chronic lung disease has received little empirical attention. To the best of our knowledge, the study described in chapter 2 was the first to document a prospective association between wellbeing and incidence of arthritis or chronic lung disease. Nevertheless, there is evidence that negative psychosocial factors are associated with a higher risk of both diseases.

Firstly, in the case of arthritis risk, Harris et al. (2013) found a significant association between perceived stress and arthritis incidence in a cohort of 12,202 Australian

women aged 45-50 years, such that women who experienced high levels of stress were 2.4 times more likely to have developed arthritis 3 years later. Three previous longitudinal studies documented an association between depressive symptoms and a higher risk of incident arthritis or joint pain (Jinks, Jordan, Blagojevic, & Croft, 2008; Palmer, Reading, Calnan, Linaker, & Coggon, 2007; Seavey, Kurata, & Cohen, 2003). In addition, several studies found an association between traumatic events in childhood (including fearful experiences, physical abuse, hospitalization and being sent away from home) and arthritis risk in adulthood. For instance, in a sample of 9,159 Canadian adults, participants (free of arthritis at baseline) who reported multiple traumatic events in childhood had a moderately increased risk of developing arthritis over the 4 year follow up period. Similar reports regarding the association between early life stressors and arthritis risk are provided by Fuller-Thomson, Stefanyk and Brennenstuhl (2009) and Von Korff et al. (2009).

Fewer studies have explored links between negative psychosocial factors and risk of chronic lung disease. However, one longitudinal study of 14,682 men and women, found that major depression at baseline was associated with a significantly higher risk of developing chronic obstructive pulmonary disease (COPD) over a two year follow up period (Patten et al., 2008). The effect size was not substantially changed by the inclusion of sex, age, health care use and smoking status (Patten et al., 2008). A second study examined the association between psychological distress and risk of COPD and found that psychological distress was associated with an increased risk of incident COPD over the 3 year follow up period in women (n = 2,203) but not in men (n = 1,682) (Pembroke, Rasul, Hart, Smith, & Stansfeld, 2006).

There are various mechanisms that could account for the link between psychosocial factors and arthritis or chronic lung disease risk. Depression or anxiety may confer an increased risk due to associations with traditional risk factors including higher levels of smoking and physical inactivity (Pembroke et al., 2006). In addition, negative psychosocial factors could impact arthritis or chronic lung disease risk via more direct physiological pathways. Previous studies have documented a link between depression or anxiety and elevated levels of inflammatory markers (Pitsavos et al., 2006; Stewart, Rand, Muldoon, & Kamarck, 2009) – which are also implicated in the aetiology and progression of arthritis and chronic lung disease (Karlson et al., 2009; Markus MJ Nielen, 2009; Masi, Aldag, & Sipes, 2001; Rovina, Koutsoukou, & Koulouris, 2013; Sokolove & Lepus, 2013).

Positive states such as high wellbeing have been linked with health protective behaviours (including physical activity) and lower levels of inflammatory biomarkers (Grant et al., 2009; Roy et al., 2010; Sin, Graham-Engeland, & Almeida, 2015; Steptoe et al., 2012; Steptoe, O'Donnell, Badrick, et al., 2008). Therefore, high wellbeing may be linked with a reduced risk of arthritis or chronic lung disease. Importantly, research indicates that the association between wellbeing and disease incidence can be partially independent of depressive symptoms (Boehm et al., 2011; Kubzansky et al., 2001; Shirom et al., 2012). Thus, wellbeing could be related to arthritis or chronic lung disease risk independently of the documented effect of negative psychosocial factors.

In the current study, we used data from a cross-national database of people aged 50 and over to test for a prospective association between wellbeing and incidence of

arthritis or chronic lung disease, while controlling for potentially mediating or confounding factors including demographic differences, health behaviours, comorbidities and depressive symptoms.

Methods

Study population

The Survey of Health, Ageing and Retirement in Europe (SHARE) is a cross-national prospective cohort study of people aged 50 and over (Börsch-Supan et al., 2008, 2013; Börsch-Supan & Alcser, 2005). Based on probability samples, SHARE is designed to be representative of the older community-dwelling population in 20 European countries and Israel. 30, 816 participants from 11 European countries (Denmark, Sweden, Austria, France, Germany, Switzerland, Belgium, the Netherlands, Spain, Italy and Greece) and Israel were recruited in the first wave of SHARE in 2004/2005. Since then, participants have been interviewed biennially. Additional countries entered the study in waves 2 and 4. SHARE has been reviewed and approved by the Ethics Committee of the University of Mannheim (Alcser et al., 2005).

Wellbeing

Wellbeing at wave 1 was assessed with the CASP-12 – an abridged version of the CASP-19 quality of life questionnaire (Hyde et al., 2003). Participants respond to 12 questions on a four point Likert scale (scored 0-3). Possible scores range from 0-48 with higher scores indicating higher levels of wellbeing. For the study sample, the CASP-12 showed high internal consistency ($\alpha = 0.82$).

Arthritis and chronic lung disease incidence

In waves 1, 2, 4 and 5, participants were asked whether a doctor had ever told them that they had 'arthritis including osteoarthritis, or rheumatism' or 'chronic lung disease such as chronic bronchitis or emphysema'. As has been done previously with SHARE (Avendano & Mackenbach, 2008), participants who did not report a diagnosis at wave 1 but reported a diagnosis in a subsequent wave were classified as incident cases. As data on date of diagnosis was not collected, for the purposes of statistical analysis, the date of the interview (month and year) at which the participant first reported a diagnosis of arthritis or chronic lung disease was taken as the date of diagnosis.

Covariates

We chose age, sex, health behaviours (physical activity, alcohol consumption and smoking status), body mass index (BMI), depressive symptoms, socio-economic status (as indexed by real household assets net of any debt), level of education and prevalent hypertension, diabetes, heart attack and stroke at wave 1 as potential confounders or mediators of the relationship between wellbeing and later arthritis or chronic lung disease incidence. Age, sex, socio-economic status, depressive symptoms, BMI and health behaviours have previously been associated with arthritis and chronic lung disease risk (Atlantis, Fahey, Cochrane, & Smith, 2013; Bengtsson, Nordmark, Klareskog, Lundberg, & Alfredsson, 2005; Buckwalter & Lappin, 2000; Costenbader et al., 2006; Di Giuseppe et al., 2012; Ellison-Loschmann et al., 2007; Felson et al., 1997, 2000; Harik-Khan, Fleg, & Wise, 2002; Harris et al., 2013; Mannino & Buist, 2007; Patten et al., 2008; Rosenberg et al., 2015; Ward &

Hubbard, 2011) as well as subjective wellbeing (Brett et al., 2012; Hanmer, Lawrence, Anderson, Kaplan, & Fryback, 2006; Martin Pinquart & Sörensen, 2000; Pressman & Cohen, 2005; Rippe et al., 1998; Sjöström et al., 1992; Steptoe et al., 2014). Hypertension, diabetes, heart attack and stroke commonly co-occur with arthritis (in particular osteoarthritis) and chronic lung disease (Barr et al., 2009; Nüesch et al., 2011). All of these conditions have been associated with lower wellbeing (Hobbs et al., 2002; Wikman, Wardle, & Steptoe, 2011). In analysis predicting chronic lung disease risk, we adjusted for several additional covariates including: pack years smoked, height and history of high cholesterol, cataracts, osteoporosis, arthritis or asthma. These variables have been linked to wellbeing and chronic lung disease risk in previous studies (Barr et al., 2009; Deaton & Arora, 2009; Rosenberg et al., 2015; Ward & Hubbard, 2011; Wikman et al., 2011).

Participants reported the frequency with which they engaged in vigorous and or moderate physical activity. There were 4 response options: ‘more than once a week’, ‘once a week’, ‘one to three times a month’ and ‘hardly ever or never’. Responses were dichotomised based on activity frequency – either once a week (or more) or less than once a week. Responses were then summed to create 3 categories: physical inactivity, moderate but not vigorous activity at least once a week and vigorous physical activity at least once a week. Participants reported their frequency of alcohol consumption, there were 7 response options: ‘almost every day’, ‘5 or 6 days a week’, ‘3 or 4 days a week’, ‘once or twice a week’, ‘once or twice a month’, ‘less than once a month’, ‘not at all in the last 6 months’. Participants reported their smoking status (non-smoker, former smoker or current smoker). For the pack years

variable, former and current smokers reported the number of cigarettes, cigars or pipes they smoked per day and the number of years they had smoked. Number of cigars and pipes per day were converted to the equivalent number of cigarettes (1 cigar or pipe = 2.5 cigarettes). We then derived the number of cigarette packs smoked per day (n of cigarettes per day/20) and multiplied the number of cigarette packs per day by the number of years smoked. The pack years variable was coded as 0 for non-smokers. The EURO-D was used to assess symptoms of depression (Prince et al., 1999). The scale was originally developed to harmonize data on depression from 11 European countries. The scale consists of 12 items – all of which are taken from the Geriatric Mental State (Copeland, Dewey, & Griffiths-Jones, 1986). Socioeconomic status was indexed by total household assets, gross value of home, value of any other real estate, value of any share of business and value of any vehicles minus mortgage of main residence. The study sample was divided into quintiles according to total household wealth. Level of education was classified according to the International Standard Classification of Education (ISCED-97) framework; participants were categorised according to their highest level of education: pre-primary (introduction into school environment e.g. nursery), primary (beginning of systematic studies of reading, writing mathematics), lower secondary (full implementation of basic skills, subjects presented by more qualified teachers than in primary education), upper secondary (begins at the end of full time compulsory education, typically requires entry qualification) post-secondary (any program designed to bridge the gap between upper secondary and first stage tertiary education), first stage tertiary (program lasting a minimum of 2 years, educational content higher than upper or post stage secondary, entry requires successful

completion of upper/post-secondary education) and second stage tertiary (programs leading to the award of an advanced stage research qualification). BMI (kg/m^2) was derived from participant self-reported height and weight. People categorised as obese have a higher risk of arthritis (Qin et al., 2015), whereas those who have a low BMI are more likely to develop chronic lung disease (Harik-Khan et al., 2002). To model the non-linear relationships between BMI and these chronic conditions, we categorized BMI according to World Health Organisation guidelines as underweight (below 18.5 kg/m^2) normal weight (18.5-24.9 kg/m^2) overweight (25-29.9 kg/m^2) and obese (30 kg/m2 or above).

Sample for analysis predicting arthritis risk

Of the 30, 816 people taking part in wave 1, 10,530 were included in analysis predicting arthritis risk. Participants were excluded if, at wave 1, they reported a diagnosis of arthritis or did not know whether they had been diagnosed with arthritis or if they refused to respond to the question (n = 5,694). Participants were additionally excluded if they only participated in wave 1 (n = 6,500) or they had missing data for wellbeing (n = 6,661) or any of the covariate variables (n = 1,431).

Sample for analysis predicting chronic lung disease risk

The sample for analysis predicting chronic lung disease risk included 12,246 participants. Participants were excluded if they reported a diagnosis of chronic lung disease at wave 1 or did not know whether they had been diagnosed with chronic lung disease or if they refused to respond to the question (n = 1,664). We additionally excluded participants who only participated at wave 1 (n = 7,363), had missing wellbeing data (n = 7,970) or had missing covariate data (n = 1,573).

Statistical analysis

Analyses were performed in RStudio 1.0.143 (RStudio Team, 2016). Cox proportional hazards regression was conducted to examine the association between wellbeing scores at baseline and incidence of arthritis or chronic lung disease over the follow-up period. On the basis of Schoenfeld residuals, we found no evidence that the proportional hazards assumption was violated (all *p* values >0.1). Survival time in days was calculated from the date of the wave 1 interview to the date of disease diagnosis or the date of the last follow up interview, whichever occurred first. Preliminary analysis predicting arthritis risk indicated that the relationship between wellbeing scores and arthritis incidence did not differ by sex (*p* for interaction terms >0.05). However, the relationship did differ by age ($p = 0.002$). Consequently, we created three age groups with a similar number of participants in each: under 60, 60-69 and 70 or over; we conducted separate Cox proportional hazards regression analysis for each age group.

Preliminary analysis predicting chronic lung disease risk indicated a significant interaction between sex and wellbeing ($p = 0.02$). Consequently, proportional hazards regression analysis was conducted for women and men separately. The relationship between wellbeing and incidence of chronic lung disease did not differ by age (*p* for interaction terms >0.05).

We used seven adjustment models, the minimally adjusted model was adjusted for sex in analysis predicting arthritis risk and age in analysis predicting chronic lung disease risk. Subsequent models additionally adjusted for each set of covariates in turn, these were: health behaviours, BMI, depressive symptoms, SES and

comorbidities (history of diabetes, hypertension, stroke and heart attack in analysis predicting arthritis risk and additionally history of high cholesterol, cataracts, osteoporosis, arthritis and asthma for analysis predicting chronic lung disease risk). We adjusted for all the covariates in the final model (model 7). In order to reduce the risk of reverse causality (i.e. undiagnosed pre-existing arthritis or chronic lung disease influencing wellbeing), the regression was repeated excluding the first two years of follow up. Hazard ratios (HR) and 95% confidence intervals (CI) are expressed according to a standard deviation (SD) increase in wellbeing score.

Missing covariate or wellbeing data may have introduced a source of bias. To address this, we repeated the main analysis using imputed wellbeing and covariate data. We used a multiple multivariate imputation technique. This approach relies on the assumption that data are missing at random – meaning that the pattern of missingness is systematic and can be predicted by observed data (Garson, 2015). We assumed data were missing at random as missingness was significantly correlated with other measured variables (Garson, 2015). Missing data were imputed for the sample of participants who took part at wave 1, did not report a diagnosis of the disease outcome (either arthritis or chronic lung disease) at wave 1 and had information on disease incidence. Imputed datasets were generated using chained equations imputation. The imputation models included survival time, disease incidence, wellbeing score and the covariates. 35 imputed datasets were generated separately for analysis predicting arthritis risk, and for analysis predicting chronic lung disease risk. The sample sizes for analysis predicting arthritis and chronic lung

disease risk were 18,622 and 21,789 respectively. Estimates from analysis with imputed data, are pooled estimates from the 35 datasets.

Table 3.1

Baseline characteristics stratified according to tertiles of wellbeing (lowest, middle and highest wellbeing) total n = 12,854

Characteristics	**Lowest**	**Middle**	**Highest**	***p*-trend**
Age (yrs.), *M* (SD)	65 (10)	63 (10)	62 (9)	<0.001
Depression score, *Mdn* (IQR)	3 (1-5)	1 (0-3)	1 (0-2)	<0.001
Net assets, *M* (*SD*) (in €100,000)	3.52 (14.63)	6.54 (23.64)	8.53 (25.57)	<0.001
Female, No. (%)	2,107 (43)	1,937 (47)	1,759 (47)	<0.001
BMI ($kg/m^{2)}$, *M* (SD)	26.89 (4.47)	26.31 (4.19)	25.92 (3.96)	<0.001
Height (cm), *M* (SD)	166.66 (8.86)	168.77 (8.94)	169.56 (8.81)	<0.001
Physical activity, No. (%)				<0.001
Physically inactive	831 (17)	305 (7)	200 (5)	
Moderate physical activity	1915 (39)	1522 (37)	1200 (32)	
Vigorous physical activity	2191 (44)	2317 (56)	2373 (63)	
Alcohol, No. (%)				<0.001
Almost every day	1202 (24)	1043 (25)	1067 (28)	
1 to 4 days a week	1044 (21)	1326 (32)	1296 (34)	
Twice a month or less	1043 (21)	913 (22)	722 (19)	
Not at all	1648 (33)	862 (21)	688 (18)	
Smoking status, No. (%)				<0.001
Smoker	1010 (20)	816 (20)	708 (19)	
Former smoker	2656 (54)	2063 (50)	1875 (50)	
Non-smoker	1271 (26)	1265 (31)	1190 (32)	

Education, No. (%)				<0.001
Pre-primary or primary	2122 (43)	1054 (25)	691 (18)	
Lower or upper secondary	2148 (44)	1989 (48)	1883 (50)	
Post-secondary,	77 (2)	133 (3)	136 (4)	
First or second stage tertiary	590 (12)	968 (23)	1063 (28)	
History of hypertension, No. (%)	1808 (37)	1252 (30)	1008 (27)	<0.001
History of diabetes, No. (%)	534 (11)	307 (7)	252 (7)	<0.001
History of stroke, No. (%)	221 (4)	117 (3)	71 (2)	<0.001
History of heart attack, No. (%)	710 (14)	449 (11)	270 (7)	<0.001
History of cholesterol, No. (%)	1126 (23)	845 (20)	679 (18)	<0.001
History of asthma, No. (%)	249 (5)	188 (5)	118 (3)	0.001
History of arthritis, No. (%)	1253 (25)	665 (16)	406 (11)	<0.001
History of osteoporosis, No. (%)	532 (11)	253 (6)	158 (4)	<0.001
History of cataracts, No. (%)	443 (9)	253 (6)	215 (6)	<0.001

[a]statistical significance is based $\chi 2$ tests or one-way ANOVA, as appropriate.

Results

Table 3.1 shows the baseline characteristics of the sample according to tertiles of wellbeing. Note that for this table, we did not exclude participants with a history of arthritis or chronic lung disease. On average, people with higher wellbeing were younger, had lower depressive symptom scores, were wealthier, had a lower BMI, were taller, were more physically active, consumed more alcohol, had a higher level of education and were less likely to report a history of chronic disease.

Table 3.2

Incident cases of arthritis and total number of participants by country.

Country		**Frequency**	**%**
Austria	Cases	199	21
	Total n	937	
Germany	Cases	185	20
	Total n	942	
Sweden	Cases	267	18
	Total n	1474	
Netherlands	Cases	186	15
	Total n	1239	
Spain	Cases	251	35
	Total n	720	
Italy	Cases	315	44
	Total n	712	
France	Cases	169	29
	Total n	592	
Denmark	Cases	171	24
	Total n	708	
Greece	Cases	90	7
	Total n	1263	
Switzerland	Cases	73	16
	Total n	452	
Belgium	Cases	387	26
	Total n	1491	

Arthritis risk

Table 3.2 displays the number of participants and incident cases of arthritis in our analysis stratified by country. The highest percentage of incident cases was reported by participants in Italy (44%), and the lowest percentage of cases was reported by participants in Greece (7%). Overall, 2,293 incident cases of arthritis were reported between waves 2 and 5. Incidence was greater in older age groups - with 18% incidence in the under 60 age group, 23% incidence in the 60-69 age group and 27% in the 70 and over age group.

Table 3.3

Hazard ratios (95% confidence intervals) for incident arthritis according to a SD increase in wellbeing score, n =10,530

Covariates	**Age group**	**HR (95% CI)**	**% Attenuation**
Sex	<60	0.71 (0.67-0.76)**	
	60-69	0.75 (0.71-0.81)**	
	70+	0.84 (0.78-0.91)**	
Sex + health behaviours	<60	0.74 (0.69-0.79)**	10%
	60-69	0.75 (0.70-0.81)**	0%
	70+	0.86 (0.80-0.93)**	12%
Sex + BMI	<60	0.72 (0.68-0.77)**	3%
	60-69	0.76 (0.71-0.82)**	4%
	70+	0.86 (0.80-0.92)**	13%
Sex + EURO-D	<60	0.78 (0.72-0.84)**	24%

	60-69	0.79 (0.73-0.86)**	16%
	70+	0.88 (0.82-0.96)*	25%
Sex + wealth + education	<60	0.75 (0.70-0.80)**	14%
	60-69	0.77 (0.71-0.82)**	8%
	70+	0.87 (0.81-0.94)**	19%
Sex + comorbidities	<60	0.71 (0.67-0.76)**	0%
	60-69	0.75 (0.70-0.81)**	0%
	70+	0.84 (0.78-0.91)**	0%
All covariates	<60	0.82 (0.76-0.89)**	38%
	60-69	0.81 (0.75-0.88)**	24%
	70+	0.93 (0.85-1.02)	56%

Table 3.3 displays the HRs for incident arthritis in the three age-groups (under 60, 60-69 and 70 or over) according to a SD increase in wellbeing score. HRs are adjusted for sex, followed by separate adjustment for health behaviours, BMI, depressive symptoms, SES, and comorbidities; the final model includes all the covariates.

Higher wellbeing was associated with a lower risk of incident arthritis after adjustment for sex in all three age groups. This reduction in risk was higher for the younger age groups. A SD increase in wellbeing score was associated with a 29% (HR: 0.71; 95% CI: 0.67-0.76) decrease in arthritis risk in the under 60 age group, a 25% (HR: 0.75 95% CI: 0.71-0.81) decrease in arthritis risk in the 60-69 age group

and a 16% (HR: 0.84 95% CI: 0.78-0.91) decrease in arthritis risk in the 70 and over age group.

The association between wellbeing and arthritis risk was attenuated by adjusting for the covariates (depressive symptoms, health behaviours, BMI category, wealth, education and comorbidities). In the fully adjusted model, a SD increase in wellbeing score was associated with an 18% (HR: 0.82 95% CI: 0.76-.89) decrease in arthritis risk in the under 60 age group and a 19% (HR: 0.81 95% CI: 0.75-0.88) decrease in arthritis risk in the 60-69 age group. The association between wellbeing score and arthritis risk was not significant in the fully adjusted model in the 70+ age group.

The association between wellbeing score and arthritis risk was most strongly attenuated by adjusting for depressive symptoms (24% in the under 60 group, 16% in the 60-69 group and 25% for the 70+ group) followed by SES (14% in the under 60 group, 8% in the 60-69 group and 19% for the 70+ group). Adjusting for health behaviours and BMI also led to a small amount of attenuation; however, adjusting for comorbidities had little effect.

The association between wellbeing score and arthritis risk was little changed by the exclusion of cases diagnosed in the first two years of follow-up or the exclusion of participants who had not reported having been diagnosed with arthritis at baseline but who did say that they were bothered by back, knee, hip or joint pain at that time. This similarity suggests the association between wellbeing scores and arthritis risk is unlikely to reflect reverse causation whereby undiagnosed arthritis at baseline affected wellbeing.

The pooled effect sizes from analysis with imputed information was very similar to those obtained from analysis employing the sample with complete data. See table 3.4 for a comparison of results.

Table 3.4

Hazard ratios (95% confidence intervals) for incident arthritis according to a SD increase in wellbeing score from analysis with imputed missing covariates (n = 13,594) and from analysis with complete data (n = 10,530).

Age Group	**Analysis**	**Model 1 HR (95%-CI)**	**Model 2 HR (95%-CI)**
<60	Imputed	0.74 (0.74-0.75)**	0.84 (0.83-0.85)**
	Complete	0.71(0.67-0.76)**	0.82 (0.76-0.89)**
60-69	Imputed	0.79 (0.78-0.80)**	0.83 (0.82-0.84)**
	Complete	0.75 (0.71-0.81)**	0.81 (0.75-0.88)**
70+	Imputed	0.84 (0.83-0.85)**	0.92 (0.92-0.93)**
	Complete	0.84 (0.78-0.91)**	0.93 (0.85-1.02)

Model 1: Adjusted for sex. Model 2: Further adjusted for total net wealth, education, comorbidities, depressive symptoms, smoking, alcohol intake, physical activity and BMI. ** p <0.001, * p <0.05

Chronic lung disease risk

Table 3.5 displays the number of participants and incident cases of chronic lung disease in our analysis stratified by country. The highest percentage of incident cases was reported by participants in Italy (10%), and the lowest percentage of cases was

reported by participants in Greece (1%). Overall, 715 incident cases were reported between waves 2 and 5.

Table 3.6 displays the HRs for incident chronic lung disease for men and women according to a SD increase in wellbeing score. People with higher wellbeing scores had a significantly lower risk of incident chronic lung disease after adjusting for age. This reduction was greater for men than for women. A SD increase in wellbeing score was associated with a 33% (HR: 0.67; 95% CI: 0.60-0.75) decrease in chronic lung disease risk in men and a 20% (HR: 0.80; 95% CI: 0.73-0.87) decrease in risk in women. This association remained significant but was attenuated in men and women after adjusting for each covariate separately. Adjusting for depressive symptoms and SES led to the highest percentages of attenuation, 25 or 15% and 20 or 15%, respectively. Adjusting for BMI and history of relevant chronic conditions led to a higher percentage of attenuation for women than for men. In the model adjusted for all covariates, the association between higher wellbeing and lower chronic lung disease risk remained significant for men (HR: 0.80; 95% CI: 0.70-0.91) but was no longer significant for women (HR: 0.91; 95% CI: 0.82-1.03).

The association between wellbeing score and chronic lung disease risk was little changed by the exclusion of cases diagnosed in the first two years of follow-up or the exclusion of participants that reported a history of asthma at wave 1.

Table 3.5
Incident cases of chronic lung disease and total number of participants by country.

Country		**Frequency**	**%**
Austria	Cases	73	7
	Total N	1018	
Germany	Cases	71	7
	Total N	1024	
Sweden	Cases	67	4
	Total N	1584	
Netherlands	Cases	74	6
	Total N	1266	
Spain	Cases	75	8
	Total N	964	
Italy	Cases	93	10
	Total N	963	
France	Cases	50	6
	Total N	799	
Denmark	Cases	71	8
	Total N	891	
Greece	Cases	15	1
	Total N	1449	
Switzerland	Cases	25	5
	Total N	487	
Belgium	Cases	101	6
	Total N	1801	

Table 3.6

Hazard ratios (95% confidence intervals) for incident chronic lung disease in women and men according to a SD increase in wellbeing score, n =12,246

Covariates	**Sex**	**HR (95% CI)**	**% Attenuation**
Age	Female	0.80 (0.73-0.87)**	
	Male	0.67 (0.60-0.75)**	
Age + health behaviours	Female	0.83 (0.76-0.92)**	15%
	Male	0.70 (0.64-0.79)**	9%
Age + BMI	Female	0.83 (0.75-0.91)**	15%
	Male	0.68 (0.61-0.76)**	3%
Age + height	Female	0.79 (0.72-0.87)**	-5%
	Male	0.69 (0.62-0.76)**	6%
Age + EURO-D	Female	0.84 (0.76-0.94)*	20%
	Male	0.72 (0.64-0.82)**	15%
Age + wealth + education	Female	0.85 (0.77-0.93)*	25%
	Male	0.72 (0.64-0.80)**	15%
Age + comorbidities	Female	0.85 (0.77-0.93)*	25%
	Male	0.70 (0.63-0.78)**	9%
All covariates	Female	0.91 (0.82-1.03)	55%
	Male	0.80 (0.70-0.91)*	39%

** p <0.001, * p <0.05

The pooled effect sizes from analysis with imputed information were similar to those obtained from analysis employing the sample with complete data. However, in analysis with imputed data, the fully adjusted HR for the association between wellbeing and chronic lung disease risk in women, was significant (HR: 0.90; 95% CI: 0.81-0.99). See table 3.7 for a comparison of results.

Table 3.7

Hazard ratios (95% confidence intervals) for incident chronic lung disease according to a SD increase in wellbeing score from analysis with imputed missing covariates (n = 21,789) and from analysis with complete data (n = 12,246).

Sex	**Analysis**	**Model 1 HR (95%-CI)**	**Model 2 HR (95%-CI)**
Women	Imputed	0.78 (0.72-0.84)**	0.90 (0.81-0.99)*
	Complete	0.80 (0.73-0.87)**	0.91 (0.82-1.03)
Men	Imputed	0.67 (0.60-0.74)**	0.82 (0.74-0.92)*
	Complete	0.67 (0.60-0.75)**	0.80(0.70-0.91)*

Model 1: Adjusted for age. Model 2: Further adjusted for total net wealth, education, height, comorbidities, depressive symptoms, smoking, pack years, alcohol intake, physical activity and BMI. ** p <0.001, * p <0.05

Discussion

In a sample representative of people aged 50 or older living in Europe, higher levels of wellbeing at baseline were associated with a reduced risk of arthritis or chronic lung disease over a 9-year follow-up period. Our findings provide further evidence of

a link between wellbeing and arthritis or chronic lung disease risk, and, identify some of the factors that may account for these risk associations.

Wellbeing and arthritis risk

The association between higher wellbeing and lower arthritis risk documented in this study, corroborates our findings in the ELSA sample, reported in chapter 2. However, in contrast with our previous findings in ELSA, we found that the strength of the association between wellbeing and arthritis risk was dependent on age – with the strongest association found in the younger age groups. Following adjustment for established risk factors, wellbeing was only associated with arthritis risk among participants younger than 70.

In this study, the inverse association wellbeing and arthritis risk was partially explained by the covariate variables. Adjusting for depressive symptoms led to the highest percentage of attenuation. Depression is negatively correlated with wellbeing, and, is positively associated with arthritis risk (Jinks et al., 2008; Palmer et al., 2007; Seavey et al., 2003). The high degree of attenuation associated with adjusting for depressive symptoms in our analysis, could indicate a certain degree of measurement overlap between the wellbeing and depressive symptom measures. Nevertheless, the association between wellbeing and arthritis risk remained significant following adjustment for depressive symptoms. This suggests that the wellbeing measure captured an aspect of psychological functioning, unrelated to depressive symptoms, which uniquely predicts arthritis risk. SES (as indexed by education level and wealth), also emerged as a confound. Research indicates that individuals with high SES generally report higher levels of wellbeing than

individuals with low SES (Martin Pinquart & Sörensen, 2000), whereas arthritis is more prevalent among individuals with low SES (Pincus, Callahan, & Burkhauser, 1987).

Adjusting for physical activity, alcohol consumption, smoking status and BMI further attenuated the association between wellbeing and arthritis risk. This result contrasts with our previous findings in ELSA – where adjusting for health behaviours and BMI did not attenuate the association between wellbeing and arthritis risk. The larger sample size and analysis by age group in the current study may in part account for this difference in results; although, cultural or population specific differences between the ELSA and SHARE samples could also play a role. Overall, the effect of controlling for BMI and health behaviours was relatively small when compared to that of controlling for depressive symptoms or SES. This may reflect the fact that the association between health behaviours and arthritis risk is complex. Firstly, OA and RA are associated with different risk factors. Obesity is only associated with increased risk of OA (Felson et al., 1997), whereas smoking appears to increase the risk of RA (Costenbader et al., 2006) but not OA (Blagojevic, Jinks, Jeffery, & Jordan, 2010). Secondly, behaviours associated with higher wellbeing may in fact increase arthritis risk. For instance, vigorous physical activity (associated with higher wellbeing in the SHARE sample) is associated with an increased risk of OA (Felson et al., 2000).

Chronic conditions previously associated with low wellbeing (Wikman et al., 2011) including cardiovascular disease, hypertension and diabetes commonly co-occur with arthritis (Nüesch et al., 2011). Surprisingly, adjusting for these comorbidities did not

attenuate the association between wellbeing and arthritis risk. Additional analysis revealed that in our sample, the prevalence rate of cardiovascular disease and diabetes was not significantly different between participants who reported a diagnosis of arthritis over the follow up period compared with those who did not. This could account for the minimal effect associated with adjusting for comorbidities. Participants diagnosed with arthritis over the follow up period were significantly more likely to report a history of hypertension at baseline (p for trend <0.001). However, previous studies suggest that the impact of hypertension on quality of life is relatively small (Hobbs et al., 2002; J. A. Singh et al., 2005).

We found that the association between wellbeing and arthritis risk was stronger among participants aged younger than 70. Arnold et al. (2014) report that onset of arthritis at older ages is associated with higher disease activity and disability compared with arthritis onset at younger ages. Our findings could reflect the fact that wellbeing is not potentially protective against the onset of these more severe forms of arthritis. However, this is the first study to report such an age effect. Harris et al. (2013), who documented an association between perceived stress and arthritis risk, did not report an age interaction. It should be noted that the age range in the Harris et al. (2013) study was significantly narrower than in our study (45-50 compared with ≥50). In chapter 2, we found no effect of age on the association between wellbeing score and arthritis risk. However, it is possible that the sample size in our previous study (n = 7,640) was not large enough to detect this interaction effect.

The association between wellbeing and arthritis risk among participants younger than 70, was not fully explained by demographic factors, health behaviours or

comorbidities. It is possible that wellbeing additionally impacts physiological processes relevant to arthritis risk or symptom expression. Higher wellbeing is associated with a reduced inflammatory response (Stellar et al., 2015; Steptoe, O'Donnell, Badrick, et al., 2008). Thus, higher wellbeing could lessen the expression of arthritic symptoms, by reducing the extent of inflammation. Alternatively, wellbeing may impact the experience rather than the expression of arthritic pain. High positive state and trait affect is associated with reduced pain perception (Rasmussen et al., 2009; Villemure, Slotnick, & Bushnell, 2003); thus, high wellbeing may reduce the experience of arthritic pain. Both mechanisms (lower inflammation or pain perception) could reduce the likelihood of an individual with high wellbeing from seeking a formal diagnosis of arthritis.

The association between wellbeing and arthritis risk could also reflect the effect of unmeasured confounds. For instance, early life experiences or perceived stress in adulthood could play a role. These negative psychosocial factors are linked to a higher risk of arthritis (Fuller-Thomson et al., 2009; Harris et al., 2013; Von Korff et al., 2009) and lower levels of wellbeing (Stafford et al., 2015; Sugiura, Shinada, & Kawaguchi, 2005). Sleep quality should also be considered as a potential confound or mediator of the association between wellbeing and arthritis risk. High wellbeing is associated with longer sleep duration (Ryff et al., 2004) and insufficient sleep has been highlighted as a potential risk factor for arthritis due to its association with increased inflammation (Haack, Sanchez, & Mullington, 2007; Irwin et al., 2008).

Wellbeing and chronic lung disease risk

The current findings build on previous reports of an association between negative psychosocial factors and chronic lung disease risk (Patten et al., 2008; Pembroke et al., 2006) by demonstrating that wellbeing may have a potentially protective effect. Our findings partially replicate those reported in chapter 2. In contrast with our previous study, we did not observe a stronger association at younger ages. However, we did find an interaction by sex. The association between wellbeing and chronic lung disease risk was stronger in men than in women. Following adjustment for established risk factors, this association was only significant among men.

The covariates included in our analysis accounted for part of the association between wellbeing and chronic lung disease risk. Depressive symptoms accounted for a large proportion of this association (between 15 and 20% depending on sex). Depression, which is negatively associated with wellbeing (Brett et al., 2012), was identified as a risk factor for chronic lung disease in a previous study (Atlantis et al., 2013). In our analysis, in a model including age, depressive symptoms and wellbeing score, depressive symptoms were not independently predictive of chronic lung disease risk. SES, which is positively associated with wellbeing (Martin Pinquart & Sörensen, 2000) and negatively associated with risk of chronic lung disease (Ellison-Loschmann et al., 2007), also accounted for a substantial proportion of the association between wellbeing and chronic lung disease risk. Adjusting for the prevalence of conditions that commonly co-occur with chronic lung disease (high cholesterol, cataracts, osteoporosis, arthritis, asthma, hypertension, diabetes, heart attack and stroke), attenuated this association further.

BMI and health behaviours including alcohol consumption, smoking status, pack years and physical activity also accounted for some of the association between wellbeing and incident chronic lung disease. This finding is as expected considering the documented association between wellbeing and health behaviours (Grant et al., 2009), and health behaviours – smoking in particular – and risk of chronic lung disease (Rosenberg et al., 2015). The percentage of attenuation associated with adjusting for these variables, was higher in the ELSA sample (19-25% compared with 13-14%) (see chapter 2); however, this difference is likely to be attributable to the fact that analysis of the ELSA and SHARE samples was stratified by different variables (age and gender respectively). Gender differences were particularly evident in the BMI and comorbidities adjusted models in SHARE. In both cases, the percentage of attenuation associated with adjusting for these variables was notably higher for women compared with men.

We observed a stronger association between wellbeing and chronic lung disease risk in men compared with women. Few studies into the association between psychosocial factors and pulmonary function or physical health, have reported a similar interaction by sex. One study into the association between personality traits and asthma incidence reported a significant effect for neuroticism in men but not women. This interaction was statistically significant. (Loerbroks, Apfelbacher, Thayer, Debling, & Stürmer, 2009). Similarly, in a meta-analysis of studies into the association between wellbeing and objective health outcomes, Howell, Kern and Lyubomirsky (2007) found a larger effect size in men for cardiovascular functioning, respiratory functioning, and longevity. Although these studies corroborate our

results, findings regarding sex differences in the association between psychosocial factors and health outcomes are far from consistent. Several studies report comparable effect sizes for men and women. These include: a prospective study into the association between stress and incidence of adult onset asthma (Rod, Kristensen, Lange, Prescott, & Diderichsen, 2012) and a cross sectional study into the association between wellbeing and a number of biological risk factors including lung function (Steptoe et al., 2012). These two studies may have been underpowered for detecting a sex interaction effect; the Rod et al. (2012) study had fewer incident cases (*n*=252) than in the current study, the Steptoe et al. (2012) study had a sample size of 7,795. However, some studies find significant interactions by sex, but in the opposite direction. For example, Feller, Teucher, Kaaks, Boeing, and Vigl (2013) found a stronger association between life satisfaction and incidence of chronic diseases (cancer, stroke and diabetes) in women. In sum, there is no a clear consensus regarding sex as a moderator of psychosocial risk factors. The studies reviewed encompass a spectrum of psychosocial factors and health outcomes. It is plausible that the sex interaction observed in our study is specific to the association between wellbeing and chronic lung disease; however, additional research specifically regarding the association between positive traits and chronic lung disease risk is needed to confirm this effect.

The association between wellbeing and chronic lung disease risk was also weaker for women in the minimally adjusted model (adjusted for age only). There are several possible explanations for this difference in effect size. Firstly, Watson et al. (2004) suggest that women experience a more severe form of chronic lung disease than men.

In 3,265 chronic lung disease patients, women reported more severe symptoms despite being younger and smoking less than male patients (Watson et al., 2004). It is possible that wellbeing is not potentially protective against this more severe form of the disease. A second possibility is that women susceptible to the effects of low wellbeing, developed chronic lung disease before the age of 50 and therefore were excluded from our sample. There is some evidence that women are more likely to suffer from early-onset chronic lung disease (Foreman et al., 2011) and report more severe symptoms at a younger age (Watson et al., 2004). However, in our sample a similar proportion of men and women reported a history of chronic lung disease at wave 1. Finally, chronic lung disease is traditionally considered a 'male' disease – mainly due to previously higher smoking rates among men (Chapman, Tashkin, & Pye, 2001). A study into sex bias in the diagnosis of COPD, revealed that primary care physicians frequently failed to diagnose women with COPD (Chapman et al., 2001). Less reliable diagnosis of chronic lung disease in women, may therefore have led to an underestimation of the association between wellbeing and chronic lung disease for women in the current study.

For the men in the sample, established risk factors, depressive symptoms and comorbidities did not fully account for the association between wellbeing and the risk of chronic lung disease. This suggests that additional mechanisms may account for the association. One possibility is that wellbeing impacts physiological processes relevant to chronic lung disease risk. This causal pathway has been proposed by Kubzansky et al. (2002). Specifically, the development and progression of chronic lung disease is associated with an abnormal inflammatory response. Wellbeing could

impact this process as previous studies have documented a significant association between positive affect and biomarkers of inflammation (Stellar et al., 2015; Steptoe, Wardle, & Marmot, 2005). However, as these studies were observational, further work is needed to establish whether this link is causal.

There are a number of additional factors (not recorded at wave 1 of SHARE) that may underlie the association between wellbeing chronic lung disease risk. Firstly, diet quality may play a role. Poor diet quality (high intake of processed meats, refined grains and sugar sweetened drinks) has been identified as a risk factor for chronic lung disease (Varraso et al., 2015) and has also been associated with low wellbeing (Grant et al., 2009). Additional psychosocial factors may also play a role, perceived stress and hostility are negatively correlated with wellbeing and have previously been associated with poorer pulmonary health (Kubzansky et al., 2006; Rod, Kristensen, Lange, Prescott, & Diderichsen, 2012). Work environment may act as a third variable confound. Factory and construction work is associated with an increased risk of chronic lung disease due to occupational exposures to vapours, gas, dust and fumes (Würtz, Aasen, Miller, & Viskum, 2014). Working in a loud or noxious environment is also associated with reduced wellbeing (Kahn, 1981; Menaghan & Merves, 1984). Finally, it is also possible that early life factors or genetics impact both lung development and wellbeing in later life. The development of lung function in infancy has been identified as a significant predictor of pulmonary health in old age (Stocks & Sonnappa, 2013). Risk factors for abnormal lung development include premature birth or low birthweight, tobacco exposure during and after pregnancy and childhood respiratory illness (Stocks & Sonnappa,

2013). Stafford et al. (2015) report that childhood illness and family psychosocial factors are related to wellbeing in early old age. The contribution of genetics to the association between wellbeing and chronic lung disease risk remains to be explored.

Strengths and Limitations

Our study had several strengths, including the large sample size, the fact that the cohort was designed to be representative of people aged 50 and over in Europe and Israel, and the availability of data on a range of potentially confounding and mediating factors. Our study also had some limitations. Firstly, information on disease diagnosis by a doctor was based on self-reports. This may have affected the accuracy of the arthritis or chronic lung disease incidence variables. However, self-report of arthritis or chronic lung disease diagnosis is generally consistent with clinically derived diagnoses (March et al., 1998; Martin, Leff, Calonge, Garrett, & Nelson, 2000). Second, the effect of reverse-causality should be considered. There is commonly a delay between the onset of arthritis or chronic lung disease symptoms and formal disease diagnosis (Chan, Felson, Yood, & Walker, 1994; Jagana, Bartter, & Joshi, 2015). Thus, undiagnosed symptoms may have impacted wellbeing. However, analysis excluding participants diagnosed with arthritis or chronic lung disease within the first 2 years of follow-up, led to a minimal change in HRs. Fourth, a substantial proportion of participants were excluded from the analysis due to missing covariate data. However, analysis with imputed missing covariate data yielded similar effect sizes to those obtained for the sample with complete data suggesting that this exclusion did not significantly bias our results. A final limitation – specifically related to analysis predicting arthritis risk – was that we were unable to

distinguish between rheumatoid arthritis and osteoarthritis. Osteoarthritis, is a degenerative joint disease caused by a breakdown of cartilage, rheumatoid arthritis on the other hand, is defined as an autoimmune inflammatory disorder. Considering this difference in pathophysiology, it is likely that the nature of the association between wellbeing and arthritis risk is qualitatively different for the two conditions.

The lack of statistical adjustment for country differences in these analyses, is a further limitation of our study. In SHARE, mean levels of wellbeing vary across countries, with highest levels reported in Switzerland, the Netherlands and Denmark and the lowest in Italy and Greece. There may also be country level differences in the precision of arthritis or chronic lung disease diagnosis. These country level differences could account for the association between wellbeing and arthritis or chronic lung disease risk, if, for instance, there is a higher prevalence of these diseases in countries with lower wellbeing. However, in our sample, the percentage of incident cases of arthritis and chronic lung disease was highest in Italy and lowest in Greece, both countries with low mean wellbeing (see tables 3.2 and 3.5). The association between wellbeing and arthritis or chronic lung disease risk might also vary as a function of cultural or population specific differences. Future studies should test for these effects.

Conclusion

Our findings in this chapter provide further evidence of an association between wellbeing and arthritis or chronic lung disease risk, and, more generally indicate that the inverse association between wellbeing and disease risk applies to a range of disease outcomes. Our results also suggest that the association between wellbeing

and arthritis risk is stronger among people below the age of 70, and that the association between wellbeing and chronic lung disease risk is stronger in men than in women. Further research is needed to confirm these effects. Interventions that help improve or maintain wellbeing could complement strategies designed to reduce the prevalence of chronic disease in older populations. However, additional work is needed to test whether the association between wellbeing and arthritis or chronic lung disease risk is causal, and, to examine whether additional lifestyle factors, early life exposures or inflammatory processes account for these risk associations.

Chapter 4: Wellbeing and Arthritis Incidence, the Role of Inflammatory Mechanisms

Introduction

Following the finding that wellbeing is predictive of health outcomes such as disease risk and longevity (Chida & Steptoe, 2008; Feller et al., 2013; Howell et al., 2007; Martín-María et al., 2017; Shirom et al., 2012; Sin, 2016; Wakai et al., 2007), several studies have explored the possibility that wellbeing directly impacts biological processes relevant to disease risk (Dockray & Steptoe, 2010). In this chapter, we focus on the link between wellbeing and inflammatory processes. Several cross-sectional studies have documented an association between high wellbeing or optimism and lower levels of inflammatory markers including interleukin (IL)-6, C-reactive protein (CRP) fibrinogen and homocysteine (Hamer & Chida, 2011; Marteinsdottir, Ernerudh, Jonasson, Kristenson, & Garvin, 2016; Roy et al., 2010; Sin, Graham-Engeland, & Almeida, 2015; Steptoe et al., 2012; Steptoe, O'Donnell, Badrick, et al., 2008). These associations are not fully accounted for by differences in demographic factors, depressive symptoms or health behaviours, suggesting that wellbeing is directly related to inflammatory systems, potentially, via prefrontal and limbic system pathways (Dockray & Steptoe, 2010).

The link between wellbeing and inflammation may be clinically significant because elevated markers of inflammation in older adults are associated with a higher risk of disease and disability (T. Singh & Newman, 2011). However, it is unclear whether the association between wellbeing and inflammatory processes translates into a

reduced risk of disease. The aim of the current study, was to test whether inflammatory processes mediate the association between wellbeing and arthritis risk.

We chose to examine the link between wellbeing and risk of arthritis for two reasons. Firstly, inflammation is implicated in the aetiology and progression of rheumatoid and osteoarthritis (Karlson et al., 2009; Masi et al., 2001; Nielen et al., 2004; Sokolove & Lepus, 2013). Thus, down regulation of inflammatory processes associated with high wellbeing could result in a reduced disease risk. Secondly, in the studies described in the previous two chapters, we found that wellbeing was associated with a lower risk of arthritis. This association remained significant although attenuated after adjusting for demographic variables, depressive symptoms, comorbidities and health behaviours.

For this study, we used data from the English Longitudinal Study of Ageing (ELSA). This dataset includes measures of two inflammatory biomarkers which have previously been related to arthritis onset or progression: C-reactive protein (CRP) (Masi et al., 2001; Nielen et al., 2004) and fibrinogen (Arvidson, Larsson, & Larsen, 2002). The ELSA dataset also includes a measure of wellbeing (CASP-19). Higher CASP-19 scores have previously been associated with lower levels of CRP and fibrinogen in women (Steptoe et al., 2012).

Our aim was to test whether levels of CRP or fibrinogen mediated the association between wellbeing and incident arthritis. The ELSA dataset currently consists of six waves of data collection. We predicted that the association between wellbeing at wave 1 and incident arthritis (over the follow up period) would be mediated by

biomarker concentrations at wave 2. In addition, we predicted that change in wellbeing over the 6 waves would be associated with arthritis risk and that this association would be mediated by change in biomarker levels.

Method

Study Population

ELSA participants are aged ≥50 and were initially recruited from the Health Survey for England database in 1998, 1999 and 2001. At wave 1 (2002-3) 11,391 core participants were recruited; since then, participants have been interviewed biennially. Refreshment samples drawn from the Health Survey for England were added at Wave 3 and 4 to maintain the representation of people aged 50-75. Currently, there are 6 waves of data available (from 2002-2012). In addition to the main interview, blood samples were taken in waves 2, 4 and 6 during a separate nurse visit. Ethical approval for all ELSA waves was provided by the London Multicentre Research and Ethics Committee. All participants gave written informed consent (Steptoe et al., 2013).

Wellbeing

Wellbeing was assessed at each wave with the CASP-19 quality of life questionnaire (Hyde et al., 2003). The CASP-19 is designed to measure wellbeing across the sub-domains of control, autonomy, self-realisation and pleasure. Participants respond to 19 questions on a four point Likert scale (scored 0-3). Possible scores range from 0 to 57 with higher scores indicating higher wellbeing. For the study sample, the internal consistency reliability at wave 1 was high ($\alpha = 0.86$).

Inflammatory biomarkers

Participants who were not taking anti-coagulant drugs and did not have clotting or bleeding disorders were invited to provide a blood sample. Fasting samples (no food or drink except water for the past 5 hours) were taken where possible (44% of the blood samples taken at wave 2 were fasting samples). Samples were assayed for high-sensitivity CRP and fibrinogen at the Royal Victoria Infirmary, Newcastle-upon-Tyne, UK. CRP concentration was measured in milligram/litre (mg/l) (normal range is 3 mg/l or less (Kushner, Rzewnicki, & Samols, 2006)) and fibrinogen was measured in grams (g/l) per litre (normal range 1.45-3.48 g/l (Oswald, Hunt, & Lazarchick, 1983)). Due to its skewed distribution, we log-transformed the CRP measure.

Incident arthritis

At wave 1, participants were asked whether a doctor had ever told them that they had 'arthritis or rheumatism'. Participants reported the month and year of their diagnosis. In subsequent waves participants were asked to report whether they had been diagnosed with arthritis or rheumatism since their last interview. If a new diagnosis was reported, participants reported the month and year of diagnosis.

Covariates

We adjusted for factors that could account for the association between wellbeing and arthritis risk. These covariates were: age, sex, depressive symptoms, socio-economic status, level of education, relationship status, health behaviours (physical activity, alcohol consumption and smoking status) and body mass index (BMI). These factors have previously been linked with wellbeing (Brett et al., 2012; Hanmer et al., 2006;

M. Pinquart & Duberstein, 2010; Pressman & Cohen, 2005; Steptoe et al., 2014), arthritis risk (Bengtsson et al., 2005; Buckwalter & Lappin, 2000; Felson et al., 1997, 2000; Harris et al., 2013) and CRP levels (Brummett et al., 2013; Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, B, 2013; X. Zhang et al., 2008). We additionally adjusted for prevalent hypertension, diabetes and cardiovascular disease (CVD) at wave 1 as these conditions commonly co-occur with arthritis (Nüesch et al., 2011) and have been linked to lower wellbeing (Wikman et al., 2011).

The eight item version of the Center for Epidemiological Studies Depression Scale (CES-D) was used to assess depressive symptoms (Steffick, 2000). Socio-economic status was indexed by total household wealth, which has been identified as the most accurate indicator of long-term socio-economic circumstances in ELSA (Banks, Karlsen, & Oldfield, 2003). Education was categorised based on highest reported level of qualification: less than O-level or equivalent, O-level or equivalent, A-level or equivalent, higher than A-level but below degree and degree level (the U.S. equivalent qualifications are the high school diploma for O-level and one year of study at college or university with a B average for A-level). Relationship status was dichotomised as having (coded 1) or not having (coded 0) a partner. Participants reported the frequency with which they engaged in vigorous, moderate and mild exercise. Response options were ‘more than once a week’, ‘once a week’, ‘one to three times a month’ and ‘hardly ever or never’. As previously (Hamer et al., 2014), responses to physical activity questions were recoded as either once a week (or more) or less than once a week. We then created four categories: physical inactivity, mild but not moderate or vigorous activity at least once a week, moderate but not vigorous

physical activity at least once a week and vigorous physical activity at least once a week. Frequency of alcohol consumption was recorded. Response options were: 'twice a day or more', 'daily or almost daily', 'once or twice a week', 'once or twice a month', 'special occasions only' and 'not at all'. Participants reported their smoking status as either 'non-smoker', 'ex-smoker' or 'current smoker'. BMI was derived from height and weight measures taken during the nurse visit at wave 0 which took place between 1998, 1999 and 2001 (there was no BMI measure at wave 1).

To summarise, we used wellbeing measures from waves 1- 6, CRP and fibrinogen measures from waves 2, 4 and 6, a BMI measure from wave 0 and all other covariate measures from wave 1.

Analytical Sample

5,266 participants were included in our sample. Participants were excluded if they reported a history of arthritis or did not know whether they had been diagnosed with arthritis at wave 1 (n = 3,721) (we excluded these participants so that the wellbeing measure preceded arthritis diagnosis). We further excluded participants if they had missing covariate data at wave 1 (n = 2,404). Missing covariate data ranged from 0.3% for educational attainment to 3% for depression. See table 4.1 for a comparison of covariates among included and excluded participants. Compared with excluded participants, participants included in our sample were younger, reported fewer depressive symptoms, were wealthier, were more likely to be female, had a higher BMI, were more physically active, drank more frequently, were more likely to have a

partner, had more years of education, were less likely to report a history of diabetes, cardiovascular disease (CVD) and more likely to report a history of hypertension.

Table 4.1.

Baseline characteristics of participants included and excluded from the analytical sample

Characteristics	**Included** **N = 5,266**	**Excluded**	**N for excluded**	***p*-trend[a]**
Age (yrs.), *M* (SD)	63.03 (9.49)	67.19 (10.82)	6,125	<0.001
CES-D score, *Mdn* (IQR)	617 (11)	1312 (20)	5,778	<0.001
BMI ($kg/m^{2)}$, *M* (SD)	27.12 (4.25)	22.78 (12.06)	5,939	<0.001
Wealth, (in £ 100,000) *M* (SD)	2.4 (4.4)	1.8 (3.2)	5,925	<0.001
Female, No. (%)	2613 (49)	3592 (59)	6,125	<0.001
Physical activity, No. (%)			5,951	<0.001
Physically inactive	310 (6)	901 (15)		
Mild physical activity	558 (11)	1111 (18)		
Moderate physical activity	2634 (50)	2651 (43)		
Vigorous physical activity	1764 (33)	1288 (21)		
Alcohol consumption, No. (%)			5,950	<0.001
At least twice a day	229 (4)	260 (4)		
Daily or almost daily	1379 (26)	1281 (21)		
Once or twice a week	1768 (34)	1610 (26)		
Once or twice a month	570 (11)	587 (10)		
Special occasions only	905 (17)	1289 (21)		
Not at all	415 (8)	923 (15)		
Smoking status, No. (%)			5,953	0.022

Smoker	952 (18)	1046 (17)		
Former smoker	2365 (45)	2867 (47)		
Non-smoker	1949 (37)	2040 (33)		
No partner, No. (%)	2162 (35)	1399 (27)		
Education, No. (%)			6,095	<0.001
Less than O-level or equivalent	2668 (47)	3841 (63)		
O-level or equivalent	1049 (19)	845 (14)		
A-level or equivalent	412 (7)	312 (5)		
Higher education below degree	721 (13)	577 (9)		
Degree level or equivalent	825 (15)	520 (9)		
History of diabetes, No. (%)	325 (6)	528 (8)	6,022	<0.001
History of CVD, No. (%)	377 (7)	714 (11)	6,022	<0.001
History of hypertension, No. (%)	1857 (33)	2573 (40)	6,022	<0.001

[a] Statistical significance is based on $\chi 2$ tests or t-tests, as appropriate.

We conducted analysis using Mplus version 7.4 (Muthén, & Muthén, 1998). We did not exclude participants with missing wellbeing or CRP data. Mplus uses all available data to estimate the model using full information maximum likelihood. This approach to handling missing data is recommended over listwise deletion, pairwise deletion, and similar response pattern imputation (Enders & Bandalos, 2001).

Analysis

We ran preliminary analysis to establish whether log-CRP or fibrinogen levels at wave 2 were associated with arthritis risk in our sample. Each biomarker was entered

separately into a Cox proportional hazards model which was additionally adjusted for age and sex. Only CRP was a significant predictor of arthritis risk ($p = 0.001$). Consequently, we only tested for mediation using CRP.

To examine the association between wellbeing or CRP with arthritis risk, we ran a Cox proportional hazards model predicting arthritis risk that included age, sex and latent variables representing wellbeing and CRP initial status (intercepts) at wave 1 and wave 2 respectively, and amount of change (slopes) in wellbeing and CRP over the follow up period (Duncan & Duncan, 2004). We used unstandardized CRP and wellbeing scores in line with Seltzer, Frank and Bryk's (1994) recommendation. Unstandardized parameter estimates are in the units of the original scale. The wellbeing slopes were defined so that slopes represented the predicted amount of change in wellbeing score every 2 years (between waves). Slopes ranged from -4.65 to 1.86 ($M = -0.69$, SD = 0.57). CRP slopes represented the predicted amount of change in log-CRP concentration every 4 years (between waves 2, 4 and 6). These slopes ranged from -0.47 to 0.32 ($M = -0.03$, SD = 0.05).

We ran mediation analysis testing two possible mediation pathways. Specifically, we tested whether the association between wellbeing at wave 1 and arthritis risk was mediated by CRP concentrations at wave 2, and, whether the association between change in wellbeing and arthritis risk was mediated by change in levels of CRP.

Mediation analysis was conducted using a maximum likelihood robust (MLR) estimator and Monte Carlo integration. We tested for mediation using a structural equation modelling approach (Lockhart, MacKinnon, & Ohlrich, 2011). This allowed

us to estimate the direct effect of wellbeing (intercept or slope) on arthritis risk and the indirect or mediated effect of wellbeing (intercept or slope) on arthritis risk through CRP (intercept or slope). Mplus uses the Delta method (MacKinnon, 2008) to calculate indirect effects and provides standard errors, confidence intervals, and significance tests. The Delta method is the same as the Sobel test, but with an added covariance term between the a and b estimates (in this case, wellbeing and CRP) (MacKinnon, 2008). The Sobel test derives a t statistic by comparing the magnitude of the indirect effect to its estimated standard error of measurement (Sobel, 1982).

We repeated this analysis additionally adjusting for wealth, education, relationship status, depressive symptoms, health behaviours, BMI and comorbidities.

Coefficients of log-transformed dependent variables were back-transformed using the formula $(e^{\beta 1}-1)*100$ and interpreted as the average percentage change in the dependent variable according to a unit increase in the independent variable. Log-transformed independent variables were back-transformed using the formula $\beta_1*\ln(1.01)$ and interpreted as the amount of change in the dependent variable according to a 1% increase in the independent variable (Vittinghoff, Glidden, Shiboski, & McCulloch, 2011).

It should be noted that we calculated slope variables for every participant using data from waves 1 to 6 in the case of wellbeing and from wavs 2, 4 and 6 in the case of CRP. Associations between slope variables and arthritis risk are therefore not prospective.

Results

There were 1,090 incident cases of arthritis between waves 2 and 6. Table 4.2 shows the number of new diagnoses reported at each wave as well as mean wellbeing score (at waves 1 to 6) and CRP concentration (mg/l) (at waves 2, 4 and 6).

Table 4.3 shows baseline characteristics of the sample according to wellbeing tertile. People with high wellbeing tended to be younger, wealthier, have a partner, were more educated, physically active, consumed more alcohol and had lower depressive symptom scores. People with high wellbeing were also less likely to be female, overweight, smoke or report a history of diabetes, hypertension or CVD.

In preliminary Cox models adjusted for age and sex, fibrinogen was not associated with arthritis risk (for a unit increase in fibrinogen the hazard ratio (HR) was 1.05; 95% confidence interval (CI) = 0.94-1.16; $p = 0.39$); however, higher levels of log-CRP were significantly associated with increased risk. (HR = 1.14 95% CI = 1.08-1.23; $p < 0.001$). Difference in median CRP concentration between participants who developed arthritis (*Mdn* = 2.00 mg/l) and those who did not (*Mdn* = 1.70 mg/l) was significant ($p < 0.001$) and similar in magnitude to the differences reported by Karlson et al. (2009) and Nielen (2004).

Table 4.2

Incident cases of arthritis, mean wellbeing score and median CRP concentration at each wave

Measure	**T1**	**T2**	**T3**	**T4**	**T5**	**T6**
Incident cases of arthritis		367	231	198	159	135
CASP-19, *M* (SD)	63.39 (7.77)	63.21 (8.03)	61.58 (8.01)	61.32 (8.17)	61.38 (8.33)	61.17 (8.08)
CRP mg/l, *Mdn* (IQR)		1.80 (0.90-3.80)		1.80 (0.90-3.80)		1.60 (0.80-3.20)

Table 4.3

Baseline characteristics stratified according to tertiles of wellbeing score (lowest, middle and highest wellbeing)

Characteristics	**Lowest**	**Middle**	**Highest**	***p*-trend[a]**
Age (yrs.), *M* (SD)	63.28 (9.90)	62.67 (9.15)	61.69 (8.47)	<0.001
CES-D Score ≥ 4, No. (%)	228 (14)	56 (4)	11 (1)	<0.001
Wealth, *M* (SD) (in £100,000)	1.95 (4.65)	2.41 (3.11)	3.30 (5.62)	<0.001
BMI (kg/m$^{2)}$, *M* (SD)	27.23 (4.46)	27.14 (4.10)	26.94 (4.07)	0.054
Female, No. (%)	351 (54)	735 (47)	855 (52)	<0.001
Physical activity, No. (%)				<0.001
Inactive	140 (9)	56 (4)	48 (3)	
Mild	229 (14)	128 (9)	92 (6)	
Moderate	816 (52)	716 (50)	785 (47)	
Vigorous	392 (25)	525 (37)	691 (43)	
Alcohol, No. (%)				<0.001
At least twice a day	58 (4)	70 (5)	82 (5)	
Daily or almost daily	375 (24)	378 (27)	490 (30)	
Once or twice a week	507 (32)	505 (35)	564 (35)	
Once or twice a month	172 (11)	150 (11)	180 (11)	
Special occasions only	321 (20)	224 (16)	199 (12)	
Not at all	144 (9)	98 (7)	101 (6)	
Smoking, No. (%)				<0.001
Smoker	353 (22)	220 (15)	222 (14)	
Former smoker	705 (45)	661 (46)	736 (46)	

Non-smoker	519 (33)	544 (38)	658 (41)	
No partner, No. (%)	496 (31)	303 (21)	348 (22)	<0.001
Education, No. (%)				<0.001
Less than O-level	840 (53)	646 (45)	648 (40)	
O-level	281 (18)	283 (20)	307 (19)	
A-level	108 (7)	99 (7)	118 (7)	
Higher education	173 (11)	187 (13)	250 (16)	
Degree level	175 (11)	210 (15)	293 (18)	
History of diabetes, No. (%)	129 (8)	75 (5)	64 (3)	<0.001
History of CVD, No. (%)	160 (10)	87 (6)	72 (4)	<0.001
History of hypertension, No. (%)	578 (36)	489 (34)	473 (29)	<0.001

[a] Statistical significance is based on $\chi 2$ tests or one-way ANOVA, as appropriate.

In the age- and sex-adjusted model (Figure 4.1), the path from wellbeing at wave 1 to CRP at wave 2 was significant. A unit increase in wellbeing score at wave 1 was associated with an average of 2% (95% CI = 2%-1%; $p < 0.001$) decrease in CRP concentration at wave 2. The path from wellbeing slope to CRP slope was also significant with a unit increase in wellbeing slope associated with an average of 6% (95% CI = 9%-5%; $p < 0.001$) decrease in CRP slope. Wellbeing at wave 1 and CRP at wave 2 were significant predictors of arthritis risk. A 1 point increase in wellbeing score was associated with a 3% decrease in arthritis risk (hazard ratio (HR) = 0.97; 95% CI = 0.96-0.98; $p < 0.001$). A 1% increase in CRP concentration at wave 2 was associated with an average of 0.002% (HR = 1.002; 95% CI = 1.001-0.002; $p <$

0.001) increase in arthritis risk. Wellbeing slope was also associatied with arthritis risk; a unit increase in wellbeing slope was associated with a 20% decrease in arthritis risk (HR = 0.80; 95% CI = 0.74-0.91; $p < 0.001$). CRP slope was not associated with arthritis risk. Mediation analysis revealed that the indirect effect of wellbeing intercept on arthritis risk via CRP intercept was significant with 1 unit increase in wellbeing associated with a 0.004% reduction in arthritis risk ($p < 0.001$). However, the indirect effect of wellbeing slope via the CRP slope was not significant. The results of this model (including fit indices) are displayed in table 4.4.

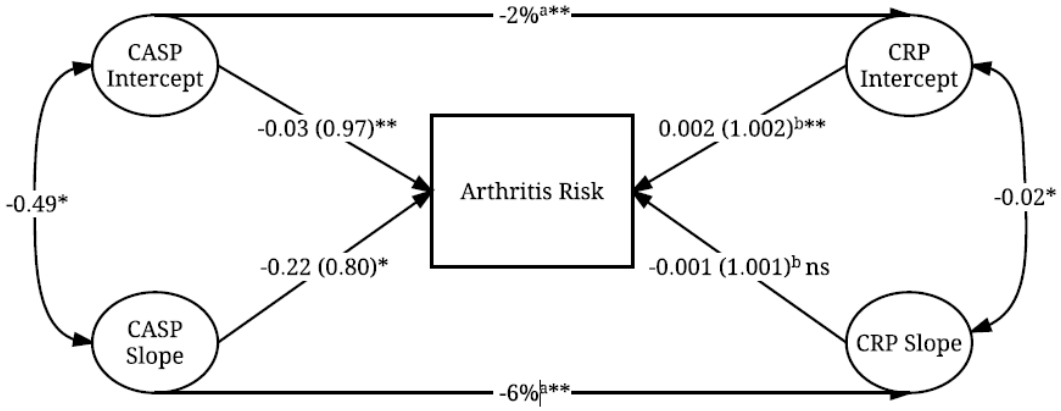

Figure 4.1

Path model adjusted for age and sex

Numbers in parentheses are exponentiated path coefficients (HRs)

[a] Coefficients have been transformed to represent percentage change in CRP intercept or slope according to a unit increase in CASP intercept or slope.

[b] Coefficients have been transformed to represent increase in arthritis risk according to a 1% increase in CRP intercept or slope.

* * = $p < 0.001$, * = $p < 0.05$, ns = $p \geq 0.05$

Table 4.4

Model 1: estimates and model fit

Path	**Estimate**	**SE**	***p*-value**
CASP-19 intercept → CRP intercept	-0.021	0.003	<0.001
CASP-19 intercept → CASP-19 slope	0.486	0.198	0.014
CASP-19 intercept → ST	-0.030	0.005	<0.001
CASP-19 slope → CRP slope	-0.066	0.009	<0.001
CASP-19 slope → ST	-0.217	0.083	0.009
CRP intercept → CRP slope	0.023	0.010	0.025
CRP intercept → ST	0.189	0.047	<0.001
CRP slope → ST	-0.019	0.877	0.98
Age → ST	-0.002	0.003	0.56
Sex → ST	0.467	0.062	<0.001

ST = survival time, number of free parameters = 27 Akaike (AIC) = 179477.447

Estimates in the model that also adjusted for wealth, education, relationship status, depressive symptoms, health behaviours, BMI and comorbidities were similar to those in the age- and sex-adjusted model. However, the association between CRP at wave 2 and arthritis risk, was attenuated (HR = 1.001; 95% CI = 1.000-1.002; p = 0.016). The association between wellbeing slope and arthritis risk was also attenuated (HR = 81; 95% CI = 0.69-0.96, p <0.001). The indirect effect of wellbeing intercept on arthritis risk via CRP intercept remained significant with a unit increase

in CASP associated with a 0.002% (p = 0.020) reduction in arthritis risk (see Figure 4.2). The results of this model (including fit indices) are displayed in table 4.5.

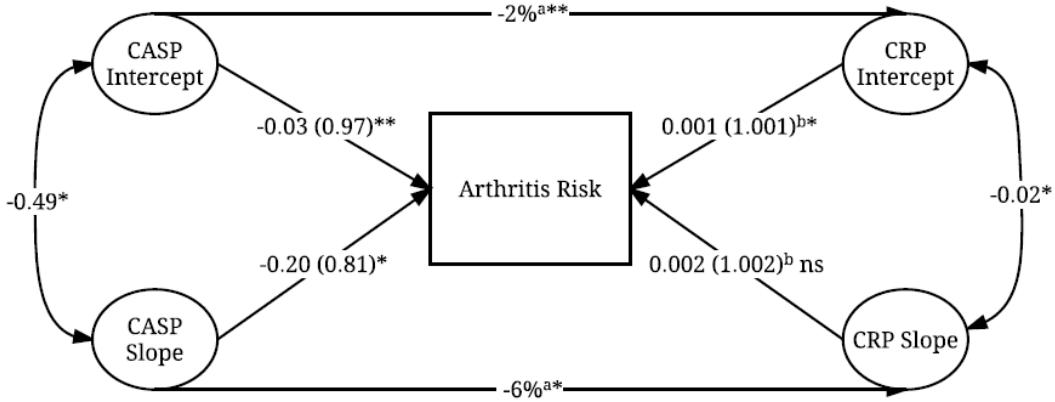

Figure 4.2

Path model additionally adjusted for depressive symptoms, demographic variables, comorbidities and health behaviours

Numbers in parentheses are exponentiated path coefficients (HRs).

[a] Coefficients have been transformed to represent percentage change in CRP intercept or slope according to a unit increase in CASP intercept or slope.

[b] Coefficients have been transformed to represent increase in arthritis risk according to a 1% increase in CRP intercept or slope.

* * = $p < 0.001$, * = $p < 0.05$, ns = $p \geq 0.05$

Additional factors signficantly associated with a higher arthritis risk in the fully adjusted model, included: being female, being diagnosed with hypertension, having a higher depressive symptom score and having a higher BMI.

Table 4.5

Model 2: estimates and model fit

Path	**Estimate**	**SE**	***p*-value**
CASP-19 intercept → CRP intercept	-0.021	0.003	<0.001
CASP-19 intercept → CASP-19 slope	-0.488	0.198	0.014
CASP-19 intercept → ST	-0.025	0.006	<0.001
CASP-19 slope → CRP slope	-0.067	0.009	<0.001
CASP-19 slope → ST	-0.203	0.085	0.017
CRP intercept → CRP slope	-0.024	0.010	0.020
CRP intercept → ST	0.121	0.050	0.014
CRP slope → ST	0.180	0.902	0.84
Age → ST	-0.001	0.004	0.75
Sex → ST	0.458	0.067	<0.001
Alcohol consumption → ST	-0.024	0.024	0.33
Education → ST	0.007	0.023	0.76
Relationship status → ST	-0.054	0.072	0.46
Smoking status → ST	-0.033	0.044	0.45
Physical activity → ST	0.032	0.040	0.42
Depressive symptoms → ST	0.041	0.018	0.022
History of hypertension → ST	0.137	0.066	0.039
History of diabetes → ST	-0.045	0.131	0.73
History of CVD → ST	-0.010	0.125	0.94
BMI → ST	0.039	0.007	<0.001
SES → ST	-0.014	0.026	0.58

ST = survival time, number of free parameters = 38, Akaike (AIC) = 179451.044

Values of CRP above 10mg/L can be caused by temporary acute or recent infections or medical trauma, and thus, may not provide a reliable measure of systemic inflammation (Pearson et al., 2003). In our sample, there were 226 cases of CRP above 10 mg/L at wave 2, 164 cases at wave 4 and 110 cases at wave 6. We re-ran the age- and sex-adjusted model excluding these cases from our sample. Again, estimates were only slightly changed from those in the original analysis. A unit increase in wellbeing intercept was associated with a 0.003% reduction in arthritis risk via the indirect pathway p <0.001.

We ran additional analysis to test for the effect of reverse causation. Firstly, to test for the effect of undiagnosed arthritis at baseline affecting wellbeing intercept, and, diagnosis of arthritis before wave 2 affecting CRP intercept), we re-ran the analysis excluding participants diagnosed with arthritis at wave 2. Results were similar to those in the original analysis; a unit increase in wellbeing intercept was associated with a 2% ($p < 0.001$) reduction in arthritis risk via the direct pathway and 0.003% reduction in arthritis risk via the indirect pathway (via CRP intercept) ($p = 0.004$). Secondly, we tested for the effect of arthritis diagnosis on wellbeing slope. For this analysis, we excluded participants who reported an arthritis diagnosis at wave 2 or wave 3, and calculated wellbeing slope using wellbeing data from waves 1 to 3 only. This allowed us to test for a prospective association between wellbeing change, from waves 1 to 3, and subsequent arthritis diagnosis reported from waves 4 to 6. Note that although CRP intercept was included in this model, CRP slope was not. For this analysis, 4,668 participants were included, and 492 incident cases of arthritis were reported. The association between wellbeing slope and arthritis risk was not

significant: HR = 0.89; 95% CI = 0.67-1.17, p = 0.392. The association between wellbeing intercept and arthritis risk was also not significant: HR = 0.98; 95% CI = 0.95-1.00, p = 0.064, while the association between CRP intercept and arthritis risk remained significant: HR = 1.11; 95% CI = 1.01-1.23, p = 0.03.

Discussion

High wellbeing is associated with a reduced risk of developing arthritis. Our aim was to test whether CRP or fibrinogen mediated this association. Only CRP was associated with arthritis risk. Our analysis revealed that the association between wellbeing at wave 1 and arthritis risk over a 10-year period was partially mediated by CRP concentration at wave 2. However, it should be noted that CRP concentration accounted for only 12% of this risk association. Although change in wellbeing over the follow up period was associated with arthritis risk, this association was not mediated by change in CRP.

The significant pathway between wellbeing at wave 1, CRP concentration at wave 2 and arthritis risk suggests that inflammatory processes are implicated in the link between wellbeing and arthritis risk. Although this mediation effect was modest, it supports the idea that wellbeing might affect disease risk via biological pathways.

Our estimate for the association between wellbeing and CRP is comparable to the association reported in a cross-sectional study in which a SD increase in quality of life score was associated with a 9.42% reduction in CRP concentration (Marteinsdottir et al., 2016). However, as in this cross-sectional study, the direction of effect between wellbeing and CRP concentration in our study is unclear. It is

possible that lower CRP concentration is a downstream consequence of high wellbeing (Ryff et al., 2004). Alternatively, inflammatory processes could impact wellbeing as inflammation has been linked to insomnia, fatigue, hostility and depression (Raison, Capuron, & Miller, 2006; Suarez, Lewis, Krishnan, & Young, 2004). It is perhaps most likely that wellbeing and CRP are reciprocally related; additional intervention studies could help quantify the extent to which wellbeing can affect CRP concentration or vice versa.

The mediation effect in our study was small because CRP concentration at wave 2 was only weakly related to arthritis risk. Deane et al. (2010) suggest that single inflammatory markers do not provide a reliable indicator of arthritis risk. This limitation may account for the weak association between CRP and arthritis risk as well as the insignificant association between fibrinogen and arthritis risk in our sample. A more accurate prediction of risk can be achieved by combining measures of multiple arthritis-related biomarkers including levels of autoantibodies and cytokines/chemokines (Deane et al., 2010). A model of the association between wellbeing and arthritis risk including these measures may reveal a stronger mediation effect than the one observed here.

We found that wellbeing and CRP slopes were significantly and inversely related – such that an increase in wellbeing between waves was associated with a decrease in CRP concentration between waves. The significant relationship between wellbeing and CRP trajectories could result from mechanisms similar to those outlined earlier. That is, change in wellbeing could cause a change in CRP concentration via psychobiological pathways, or, change in physical symptoms (for instance, chronic

pain or disability) associated with levels of inflammation could affect an individual's sense of wellbeing. However, we did not control for the effect of arthritis or other disease diagnosis on wellbeing and CRP change. Thus, it is unclear whether the association between wellbeing and CRP is causal. Disease incidence could independently impact levels of wellbeing and inflammation. Future studies should test for this effect.

A decline in wellbeing over the follow up period was associated with an increase in arthritis risk; however, the timing of arthritis diagnosis in relation to wellbeing change was not factored into our model. Thus, the direction of association is unclear. In subsidiary analysis, we tested whether change in wellbeing was prospectively associated with arthritis risk. We found that change in wellbeing between waves 1 and 3 did not predict subsequent arthritis risk. This suggests that the association observed in our original model, could have resulted from reverse causation i.e., arthritis diagnosis negatively impacting subsequent wellbeing.

CRP change did not mediate the association between wellbeing change and arthritis risk. This is because change in CRP was not related to arthritis risk. Further work is needed to establish the timing between change in CRP concentration and the onset of arthritic symptoms (van Steenbergen, Huizinga, & van der Helm-van Mil, 2013). However, there is some indication that elevation in CRP concentration can precede the onset of symptoms by up to 20 years (Masi et al., 2001). It is possible that the 8-year follow-up period (waves 2-6) in our study was too short to capture changes in CRP concentration relevant to arthritis risk. In addition, CRP was only assessed on 3 occasions at four year intervals. More frequent assessment of CRP over a longer

period would provide a more accurate index of CRP change. Finally, participants who left the study before wave 6 had significantly higher levels of CRP at wave 2 than participants who remained in the study. This pattern of attrition could have resulted in an underestimation of the association between CRP or CRP change and arthritis risk in our study as participants who left the study may have had a higher risk of arthritis.

Analysis excluding participants diagnosed with arthritis at wave 2 yielded similar results – indicating that our findings regarding the association between wellbeing and CRP level and arthritis risk are unlikely to reflect the effect of reverse causation (undiagnosed arthritis affecting reports of wellbeing at wave 1).

Our findings should be interpreted with caution as this study had some limitations. Excluding a significant proportion of participants from our sample (due to missing covariate data at wave 1) may have introduced a source of selection bias. Participants excluded from our sample differed to those included on several covariate variables (see table 4.1). In addition, arthritis incidence was ascertained using self-report. Although access to medical records would have been preferable, there is evidence that self-report of arthritis diagnosis is consistent with clinically derived measures (March et al., 1998). Wellbeing was assessed 6 times on a biennial basis, whereas CRP measures were taken on 3 occasions at 4 year intervals. Consequently, estimates of change in wellbeing may be more accurate than estimate of change in CRP. A further potential limitation, is that we did not exclude very high values of CRP from our main analysis. However, age- and sex-adjusted estimates from analysis excluding cases of CRP higher than 10mg/L were similar to those from analysis including these

cases. Finally, we were unable to distinguish between cases of rheumatoid arthritis and osteoarthritis. It is likely that the mechanisms underlying the association between wellbeing and rheumatoid or osteoarthritis are qualitatively different because these conditions involve distinct pathophysiological processes. It may be that inflammatory processes play a greater role in mediating the association between wellbeing and rheumatoid arthritis, as this condition is associated with higher levels of inflammation than osteoarthritis (Sokolove & Lepus, 2013). Our study also had several strengths. The sample size was large and we could control for many possible confounds.

In summary, our results indicate that CRP concentration mediates the association between wellbeing and arthritis risk (after taking demographic and health behaviour differences into account). Although the magnitude of this mediating effect was small, we believe our findings have theoretical implications. Specifically, they provide a proof of principle that biological processes can partially mediate the link between wellbeing and disease risk. CRP concentration represents a small component of a dynamic and interactive biological system. A combination of multiple measures of biological function would enable researchers to assess the clinical significance of the pathway between wellbeing, psychobiological processes and disease risk (Kubzansky, Boehm, & Segerstrom, 2015). We hope that our findings will help motivate this line of investigation.

Chapter 5: The Interaction between Individualism and Wellbeing in Predicting Mortality

Introduction

As we outlined in previous chapters, numerous studies document links between wellbeing or positive affect and favourable health outcomes (Boehm et al., 2011; Chida & Steptoe, 2008; Feller et al., 2013; Martín-María et al., 2017; Wakai et al., 2007). What is, however, unclear, is the extent to which these associations are largely consistent across cultures that differ in cultural dimensions related to social networks. In this chapter, we considered culture as a potential moderator of the association between wellbeing and longevity.

Culture can be defined as a shared set of values, beliefs or behaviours that differentiate one society from another (Hofstede, Hofstede, & Minkov, 1991). One dimension used to describe cultural differences is that of individualism/collectivism. In relatively collectivistic cultures, such as China, social interdependence and group loyalty is valued highly. On the other hand, in relatively individualistic cultures, such as the United States, people prioritise their personal interests over those of the wider group into which they are born (Hofstede, 2010).

The degree to which cultures are individualistic versus collectivistic may moderate the association between wellbeing and health. Comparisons of cultures has revealed that individualism/collectivism is associated with the way in which wellbeing is appraised by individuals. For instance, people in individualistic cultures prioritise positive emotions and personal wellbeing (Ahuvia, 2002; Diener & Suh, 2000;

Steptoe, Tsuda, & Tanaka, 2007; Veenhoven, 1999) and view negative emotions as harmful and undesirable (Wierzbicka, 1994). By contrast, people in more collectivistic cultures acknowledge the importance of experiencing both positive and negative emotions, and value emotional stability rather than positive affect (Lu, 2001; Ng, Ho, Wong, & Smith, 2003). Comparisons between more individualistic and more collectivistic cultures has also revealed that, in more individualistic cultures, the wellbeing of individuals is most strongly related to their self-esteem and sense of personal achievement, and that, in more collectivistic cultures, wellbeing is most strongly related to interpersonal goals and being able avoid social conflict (Uchida & Oishi, 2016). The relationship between positive and negative affect is also culturally dependent. Specifically, the size of the inverse association between positive affect and depressive symptoms is stronger in individualistic than in collectivistic cultures (Leu, Wang, & Koo, 2011).

The idea that culturally-dependent appraisals of emotion might moderate the association between emotions and health has been discussed in the context of negative affect. Two studies tested whether the strength of association between negative affect and health (the number of chronic conditions or levels of inflammatory biomarkers) differed in American and Japanese samples (Curhan et al., 2014; Miyamoto et al., 2013). Both Curhan et al. (2014) and Miyamoto et al. (2013) found that the association between negative affect and health was stronger among American participants. Based on their findings, these two groups of authors concluded that the American tendency to conceptualize negative affect as harmful and a personal responsibility may cause individuals who experience frequent

negative affect to experience additional distress, which, consequently, leads to poorer physical health (Collins et al., 2009; Rugulies, 2002; Saz & Dewey, 2001)

Cultural differences in the evaluation of wellbeing could also impact the link between wellbeing and health. Specifically, a more positive evaluation of high wellbeing in individualistic cultures (Ahuvia, 2002; Diener & Suh, 2000; Steptoe, Tsuda, et al., 2007; Veenhoven, 1999) may confer greater health benefits in these cultures via the association between positive affect and both improved physiological functioning (Steptoe & Wardle, 2005) and healthier lifestyle choices (Grant et al., 2009). Furthermore, an emphasis on personal wellbeing in individualistic cultures may cause individuals with low wellbeing to feel distressed (Leu et al., 2011), which may impact negatively these individuals' health. A more negative appraisal of low wellbeing in individualist cultures may also result in harmful coping practices, including smoking or excessive alcohol consumption (Verger, Lions, & Ventelou, 2009). Both mechanisms acting together – improved health resulting from a more positive evaluation of high wellbeing or poorer health resulting from a more negative evaluation of low wellbeing – would be expected to result in a stronger association between wellbeing and health in more individualistic cultures.

In addition to differences in the appraisal of wellbeing, cross-cultural differences in the determinants of wellbeing could modify the association between wellbeing and health. Specifically, this association should be stronger in cultures where the determinants of wellbeing are more closely linked to good physical health. However, as the determinants of wellbeing in individualistic cultures (e.g. self-esteem) and collectivistic cultures (e.g. social ties) are both associated with favourable health

outcomes and behaviours (Holt-Lunstad et al., 2010; Stamatakis et al., 2004), it is unclear which pattern of association should result in a stronger link between wellbeing and health.

Although previous studies have demonstrated that there are differences in the association between affect and health across cultures (Curhan et al., 2014; Miyamoto et al., 2013), these studies do not rule out possible confounds, including, for example, country-level differences in demographics, access to health care, life expectancy, diet, gross domestic product (GDP), and genetic make-up. This is highlighted by a recent study that found that cross-sectional associations between positive affect and self-rated health were stronger in low GDP countries (Haiti, Rwanda, Nigeria, Sierra Leone and Malawi) than in high GDP countries (United States, Ireland, Switzerland, Austria and Japan) (Pressman, Gallagher, & Lopez, 2013).

For our current study, we tested whether cross-cultural differences in the degree to which countries were individualistic led to differences in the association between wellbeing and self-rated health (a subjective health measure) or mortality risk (an objective health measure). Specifically, considering the emphasis placed on wellbeing in individualistic cultures, we predicted that the association between wellbeing and health would be stronger in more individualistic countries. To rule out competing, non-cultural hypotheses to the greatest extent possible, we took two steps. First, we examined the strength of these associations across only European countries as doing so enabled us to compare countries that varied in their levels of individualism versus collectivism, but which were comparable in other factors. For instance, although Greece is a highly collectivistic country (even more so than Japan)

and Italy is an individualistic country (only slightly less so than the United Kingdom) (Hofstede et al., 1991), Greece and Italy are similar in terms of their health care systems (Health Consumer Powerhouse, 2006), average life expectancies (Jakubowski & Busse, 1998) and diet (Trichopoulou, Naska, & Costacou, 2002). Second, we statistically controlled for differences in socio-economic status, education, health behaviours and country-level differences in healthcare provision.

Our study improved on previous research in another way, too. Previous cross-culture studies on wellbeing and health have been cross-sectional (Pressman et al., 2013). Consequently, it is unclear whether between country differences in the association reflect differences in how affect impacts physical health or *vice versa*. The present study, on the other hand, was based on longitudinal data. We therefore were able to test the association between wellbeing and subsequent mortality over a 10-year period, and control for baseline chronic disease prevalence.

Methods

Study population

30,816 participants aged 50 and over who lived in Austria, Belgium, Denmark, France, Germany, Greece, Israel, Italy, the Netherlands, Sweden, Switzerland, and Spain were recruited in the first wave of the Survey of Health Ageing and Retirement in Europe (SHARE) in 2004/2005. Since then, participants have been interviewed biennially. The SHARE project has been reviewed and approved by the Ethics Committee of the University of Mannheim (Alcser et al., 2005).

Wellbeing

Wellbeing at wave 1 was assessed with the CASP-12, which is an abridged version of the CASP-19 (Hyde et al., 2003), which was developed to measure the wellbeing of the SHARE sample. The CASP-12 asks participants to indicate the frequency with which 12 statements (e.g., I look forward to each day) apply to their life. Responses on these statements were made on a four point Likert scale ranging from 'never' to 'often'. The raw CASP-12 wellbeing scores therefore ranged from 0 to 48 with higher scores indicating higher wellbeing. For the 13,596 participants in our study sample, internal consistency for the CASP-12 was high ($\alpha = 0.83$). CASP-12 scores were relatively stable over approximately 9 years: the re-test correlation coefficient between scores at wave 1 and wave 5 was $r = 0.52$, $p < 0.001$.

Country individualism

We assigned each of the 11 countries an individualism score according to Hofstede, Hofstede and Minkov's (2010) cultural dimension of individualism (see table 5.1). The individualism score reflects the extent to which people are integrated into groups and the emphasis placed on the interests of the individual versus the group. These cultural dimension scores were originally developed using responses to a questionnaire on work-related values, collected between 1967 and 1973, from IBM employees in 40 different countries. By factor analysing mean country level responses to each question, Hofstede identified 4 cultural dimensions: power/distance, collectivism/individualism, femininity/masculinity, and uncertainty /avoidance. IBM questionnaire items related to the individualism dimension included the extent to which the respondent valued having a job that was respected by family

and friends, and having sufficient time for personal and home life. Hofstede, Hofstede and Minkov's (1997) cultural dimensions are a popular tool in intercultural research (Dahl, 2004), and have previously been used in cross-national studies of European countries (e.g., De Mooij & Hofstede, 2002). The validity of the measure has been repeatedly demonstrated (Hoppe, 1990; Merritt, 2000; Shane, 1995).

Self-rated health

At wave 1, participants were asked to report whether their health was 'very good', 'good', 'fair', 'bad' or 'very bad'. As only a small number of participants described their health as very bad (n = 178), we grouped these participants and participants who described their health as bad in the same category. Categories were coded 1 to 4 with 1 representing very good health and 4 representing bad or very bad health. For the analysis, self-rated health was treated as an ordered categorical variable.

Mortality

Participant deaths were recorded from wave 1 onwards. Deaths were confirmed by a proxy respondent (family member, a household member or a neighbour) who reported the date and main cause of death. The categories for cause of death included 'cancer', 'heart attack', 'stroke', 'other cardiovascular related illness', 'respiratory disease', 'disease of the digestive system', 'severe infectious disease', 'accident' and 'other'.

Table 5.1

Country individualism scores

Country	Individualism score	Individualism tertile
Greece	35	Low
Spain	51	Low
Austria	55	Low
Germany	67	Low
Switzerland	68	Moderate
France	71	Moderate
Sweden	71	Moderate
Denmark	74	Moderate
Belgium	75	High
Italy	76	High
Netherlands	80	High

Confounding variables

We adjusted for several variables that might confound or mediate the association between wellbeing and mortality risk. These included age, sex, socioeconomic status (SES), level of education, depressive symptoms, marital status and history of cancer, heart attack, stroke, diabetes, chronic lung disease or any long-term health problems including long term illness, disability or infirmity. Older age, male gender, lower socioeconomic status and history of chronic disease or long term disability are established mortality risk factors (Case & Paxson, 2005; Kesteloot & Huang, 2003; Krieger, Williams, & Moss, 1997; Majer, Nusselder, Mackenbach, Klijs, & van Baal,

2011; Riley & Cowan, 2014; Sorlie, Backlund, & Keller, 1995). Moreover, previous studies have documented an association between negative affect and mortality risk (Saz & Dewey, 2001) as well as an association between marital status and mortality risk (Johnson, Backlund, Sorlie, & Loveless, 2000). Age, sex, socioeconomic status, level of education, depressive symptoms, marital status and history of chronic disease or long term health problems have also been related to subjective wellbeing (Brett et al., 2012; Hanmer et al., 2006; Martin Pinquart & Sörensen, 2000; Pressman & Cohen, 2005; Steptoe et al., 2014; Wikman et al., 2011).

Socioeconomic status was indexed by total household assets, gross value of home, value of other real estate, value of any share of business and value of any vehicles minus mortgage of main residence. For the purposes of the analysis, we divided the sample into quintiles according to total household wealth. Using the International Standard Classification of Education (ISCED-97) framework, participants' educational achievement was categorised according to their highest level of education: Pre-primary or primary, lower secondary, upper or post-secondary and first or second stage tertiary. To assess history of chronic illness, participants were asked whether a doctor had ever told them that they had any of the following conditions: 'a heart attack including myocardial infarction or coronary thrombosis or any other heart problem including congestive heart failure', 'a stroke or cerebral vascular disease', 'diabetes or high blood sugar', 'chronic lung disease such as chronic bronchitis or emphysema', 'cancer or malignant tumour, including leukaemia or lymphoma, but excluding minor skin cancers'. Participants were additionally asked whether they had 'any long-term health problems including illness, disability

or infirmity'. The EURO-D was used to assess symptoms of depression (Prince et al., 1999). The scale consists of 12 items taken from the Geriatric Mental State scale (Copeland et al., 1986). Finally, participants were asked to report their marital status as 'living with spouse', 'living with partner' or 'living as a single'. We used these responses to create two categories: living alone and living with partner or spouse.

To control for country-level differences in healthcare provision, we obtained each country's health consumer index score from the Health Consumer Powerhouse (2006) report. This report assigns countries scores based on 28 indicators, including access to treatment, waiting times and health outcomes. Higher scores indicate a higher quality healthcare system; the health consumer index scores in our sample ranged from 576 (France) to 471 (Italy), the mean score was 517, which was closest to the score for Belgium (533).

Mediating variables

We chose health behaviours (physical activity, alcohol consumption and smoking status) and body mass index (BMI) as potential mediators of the relationship between wellbeing and mortality risk. Both BMI and health behaviours have been associated with mortality risk (Ford, Zhao, Tsai, & Li, 2011; Prospective Studies Collaboration, 2009) and wellbeing (Pressman & Cohen, 2005; Rippe et al., 1998; Sjöström et al., 1992; Steptoe et al., 2014).

Participants reported the frequency with which they engaged in vigorous and or moderate physical activity using one of 4 responses: 'more than once a week', 'once a week', 'one to three times a month' and 'hardly ever or never'. Responses were

dichotomised based on activity frequency – either once a week (or more) or less than once a week. Responses were summed to create 3 categories: physical inactivity, moderate but not vigorous activity at least once a week and vigorous physical activity at least once a week. Participants reported their frequency of alcohol consumption as '5 days a week or more', '1 to 4 days a week', 'twice a month or less' or 'not at all'. Participants reported their smoking status as 'non-smoker', 'former smoker' or 'current smoker'. BMI (kg/m^2) was derived from participant self-reported height and weight, and participants were categorised as underweight (below 18.5), normal weight (18.5-24.9), overweight (25-29.9) or obese (30 or above).

Analytical sample

Of the 30,816 participants, 13,596 were included in the analysis. Participants were excluded if they had missing data for wellbeing (n = 12,140) or had missing data on any of the covariates (n = 5,080). Missing covariate data ranged from 0.5% for long term illness to 8% for SES. Participants excluded because they were missing wellbeing data were older, more likely to be female, were less physically active, consumed less alcohol, were less likely to smoke, had fewer years of education and were more likely to report a history of diabetes, stroke or heart attack. These participants also had a higher depression score and were lower in socioeconomic status. Analysis comparing baseline covariates between participants with available and unavailable vital status data at wave 5, indicated that, compared with participants with vital status data, participants with missing vital status had significantly lower wellbeing, lower depressive symptoms score, lower SES, fewer years of education, were more physically active, were more likely to be a current smoker, drink more

alcohol and were less likely to report a history of cancer, heart attack or long-term illness.

11,595 participants were included in analysis predicting mortality from cardiovascular disease and 12,691 for analysis predicting mortality from cancer. Participants were excluded from this analysis if they reported a history of the relevant chronic disease at baseline: history of cardiovascular disease and cancer, respectively.

Statistical analysis

Analyses were performed in RStudio 1.0.143 (RStudio Team, 2016). We first tested whether the cross-sectional association between wellbeing and self-rated health varied across countries that differed in individualism. To these ends we used an ordinal logistic regression with self-rated health as the outcome. We also included a term for the individualism score × wellbeing score interaction in the model. A significant interaction would support the hypothesis that the association between wellbeing and self-rated health varies as a function of individualism. This model was additionally adjusted for age, sex, socioeconomic status and health care index.

Cox proportional hazards regression was used to examine the association between wellbeing at baseline and mortality over the follow-up period. Inspection of Schoenfeld residuals suggested that the proportional hazards assumption was not violated (all p-values > 0.1). We also tested for multicollinearity by calculating a variance inflation factor for each of the predictor variables in our model. This was achieved by regressing each predictor variable in turn on all remaining predictor

variables and then using the R^2 value to calculate the variance inflation factor using the formula $1/(1-R^2)$. All variance inflation factor scores were below 3 indicating that there was no multicollinearity. Survival time in days was calculated from the wave 1 interview date to the date of death or, for participants who did not die over the follow-up, the date of last follow-up interview.

We tested whether the association between wellbeing and mortality varied according to country individualism score by including the individualism score × wellbeing score interaction in a model that adjusted for age, sex, socioeconomic status and health care index score.

We adjusted for potentially confounding and mediating variables in three stages. In the first stage, we adjusted for age and sex in the model. In the second stage, we adjusted for age, sex, and the potential confounds (socioeconomic status, country level health care index score, level of education, depressive symptoms, marital status and history of cancer, heart attack, stroke, diabetes, chronic lung disease or any long-term health problems). In the third stage, we additionally adjusted for potentially mediating variables (smoking status, physical activity, alcohol consumption and BMI).

To test whether individualism moderated the association between wellbeing and cause-specific mortality, we repeated the Cox proportional hazards regression replacing all-cause mortality with mortality from cardiovascular disease or cancer.

Finally, to test for possible bias due to missing data, we used multiple multivariate imputation to impute values of covariates with missing values using IBM SPSS

Statistics 21 software. This approach assumes that data are missing at random, that is, the pattern of missingness is systematic and can be predicted by observed data (Garson, 2015). We assumed data were missing at random as missingness was significantly correlated with other measured variables (Garson, 2015). The imputation models included survival time, all-cause mortality and the covariate variables. Missing data were imputed for the sample of participants that took part at wave 1. We generated 35 imputed datasets using chained equations imputation.

Results

Table 5.2 shows the baseline characteristics of the sample (n = 13,596) according to wellbeing tertile. Overall, people with higher wellbeing were younger, had lower depressive symptom scores, were wealthier, were more likely to be male, were less likely to be overweight, were more physically active, consumed more alcohol, were less likely to be a current smoker, were more educated, were less likely to live alone and were less likely to report a history of chronic disease or long-term illness (except for history of cancer, which was not associated with wellbeing).

Table 5.2

Baseline characteristics stratified according to tertiles of wellbeing score (low, moderate and high) total n = 13,596

Characteristics	**Lowest**	**Middle**	**Highest**	**p-trend[a]**
Age (yrs), *M* (SD)	65 (10)	63 (10)	62 (9)	<0.001
EURO-D score, *Mdn* (IQR)	3 (1-5)	2 (1-3)	1 (0-2)	<0.001
Wealth (in €100,000), *M* (SD)	3.27 (13.10)	6.24 (23.19)	8.44 (25.23)	<0.001
Female, No. (%)	2611 (57)	2725 (53)	2070 (53)	<0.001
BMI (kg/m2)				<0.001
Underweight	72 (2)	61 (1)	27 (1)	
Normal weight	1586 (34)	1942 (38)	1743 (45)	
Overweight	1920 (42)	2277 (44)	1604 (41)	
Obese	978 (21)	859 (17)	528 (14)	
Physical activity, No. (%)				<0.001
Physically inactive	876 (19)	422 (08)	211 (05)	
Moderate physical activity	1767 (39)	1897 (37)	1246 (31)	
Vigorous physical activity	1913 (42)	2820 (55)	2445 (62)	
Alcohol, No. (%)				<0.001
5 days a week or more	1087 (24)	1301 (25)	1106 (28)	
1 to 4 days a week	912 (20)	1583 (31)	1332 (34)	
Twice a month or less	933 (20)	1143 (22)	745 (19)	
Not at all	1624 (36)	1112 (22)	719 (18)	
Smoking status, No. (%)				<0.001
Non-smoker	2465 (54)	2564 (50)	1931 (49)	

Former smoker	1156 (25)	1546 (30)	1228 (31)	
Smoker	935 (21)	1029 (20)	743 (19)	
Education, No. (%)				<0.001
Pre-primary or primary	2048 (45)	1367 (27)	716 (18)	
Lower secondary,	838 (18)	939 (18)	740 (19)	
Upper or post-secondary	1155 (25)	1701 (33)	1342 (34)	
First or second stage tertiary	515 (11)	1132 (22)	1104 (28)	
Self-rated health				<0.001
Very good	395 (9)	1011 (20)	1361 (35)	
Good	1644 (36)	2603 (51)	1948 (50)	
Fair	1769 (39)	1292 (25)	533 (14)	
Bad or very bad	747 (16)	233 (5)	60 (2)	
Living alone, No. (%)	1331 (29)	1135 (22)	740 (19)	<0.001
History of heart attack, No. (%)	707 (16)	555 (11)	280 (07)	<0.001
History of stroke, No. (%)	227 (05)	148 (03)	74 (02)	<0.001
History of diabetes, No. (%)	521 (11)	394 (08)	263 (07)	<0.001
History of cancer, No. (%)	253 (06)	271 (05)	192 (05)	0.43
History of lung disease, No. (%)	331 (07)	214 (04)	109 (03)	<0.001
History of disability, No. (%)	2656 (58)	2325 (45)	1438 (37)	<0.001

[a] Statistical significance is based $\chi 2$ tests or one-way ANOVA, as appropriate.

Firstly, we tested whether the association between wellbeing and self-rated health was consistent across cultures. Of the 13,596 participants in our study sample, 2,767 reported having very good health, 6,195 reported having good health, 3,594 reported having fair health and 1,040 reporting having bad or very bad health. The wellbeing

× individualism interaction was significant (p <0.001). To illustrate this interaction, we divided the sample into tertiles according to the individualism of the country in which they lived (see table 5.1 for a summary of countries in each tertile) and conducted an analysis for each group separately (see table 5.3).

Table 5.3

Proportional odds ratios (95% confidence intervals) of worse self-rated health according to a SD increase in wellbeing score, n = 13,596 [a]

Model	**Individualism tertile**	**OR (95% CI)**
Age and sex	Low	0.50 (0.47-0.52)**
	Moderate	0.38 (0.35-0.41)**
	High	0.41 (0.38-0.43)**
Confounding and mediating variables [b]	Low	0.62 (0.60-0.66)**
	Moderate	0.55 (0.50-0.60)**
	High	0.57 (0.53-0.61)**

[a] p for wellbeing score × individualism score interaction <0.001

[b] Confounding variables = socioeconomic status, country level health care index score, level of education, depressive symptoms, marital status and history of chronic disease or any long term health problems. Mediating variables = health behaviours and BMI, * p <0.05, ** p <0.001

In the sex- and age-adjusted models, the association between higher wellbeing score and better self-rated health was significant for all three groups; however, this association was weaker in the lowest individualism tertile (OR = 0.50; 95% CI =

0.47-0.52) compared with the moderate (OR = 0.38; 95% CI = 0.35-0.41) and high (OR = 0.41; 95% CI = 0.38-0.43) individualism tertiles. The association between wellbeing and self-rated health remained significant in the fully-adjusted model. Again, this association was weakest in the lowest individualism tertile (OR = 0.62; 95% CI = 0.60-0.66) compared to the moderate (OR = 0.55; 95% CI = 0.50-0.60) and high (OR = 0.57; 95% CI = 0.53-0.61) individualism tertiles.

Next, we examined the association between wellbeing and mortality risk. 1,405 deaths were reported between wave 1 and wave 5. The interaction between individualism score and wellbeing was not significant (p = 0.15); consequently, we report HRs for the whole sample. Table 5.4 displays hazard ratios (HRs) for all-cause mortality according to a standard deviation (SD) increase in wellbeing. In the age- and sex-adjusted model a SD increase in wellbeing was associated with a 22% decrease in mortality risk. This association remained significant although attenuated following adjustment for potentially confounding variables (depressive symptoms, socioeconomic status, health care index score, education, marital status and history of chronic disease or long-term illness), HR = 0.87; 95% CI = 0.82-0.93 and additional adjustment for potentially mediating variables (health behaviours and BMI), HR = 0.92; 95% CI = 0.86-0.97. In addition to wellbeing, younger age, being female, no history of chronic disease or long term illness, having a BMI of 18.5 kg/m^2 or above (compared with a BMI below 18.5), being a non-smoker (compared with current smoker) and engaging in moderate or vigorous activity were all associated with reduced mortality risk.

Table 5.4

Hazard ratios (95% confidence intervals) for all-cause mortality according to a SD increase in wellbeing score, n =13,596 [a]

Model	**HR (95% CI)**
Age and sex	0.78 (0.74-0.82)**
Confounding variables [b]	0.87 (0.82-0.93)**
Confounding and mediating variables [c]	0.92 (0.86-0.97)*

[a] *p* for wellbeing score × individualism score interaction = 0.15

[b] Confounding variables = socioeconomic status, country level health care index score, level of education, depressive symptoms, marital status and history of chronic disease or any long term health problems.

[c] Mediating variables = health behaviours and BMI

* $p < 0.05$, ** $p < 0.001$

There were 274 cardiovascular disease related deaths over the follow-up period. Our analysis revealed that the wellbeing × individualism interaction was significant ($p = 0.01$). Consequently, we divided the sample into tertiles according to individualism score and conducted analysis for each group separately. Table 5.5 displays HRs for mortality from cardiovascular disease according to a SD increase in wellbeing in each tertile. In the age- and sex-adjusted model, the association between wellbeing and cardiovascular mortality risk was significant for all three groups. A SD increase in wellbeing was associated with a 16% (HR = 0.84; 95% CI = 0.72-0.98) decrease in cardiovascular mortality risk in the tertile with low individualism scores, a 25%

(HR = 0.75; 95% CI = 0.58-0.97) decrease in cardiovascular mortality risk in the tertile with moderate individualism scores and a 39% (HR = 0.61; 95% CI = 0.50-0.76) decrease in cardiovascular mortality risk in the tertile with high individualism scores. After adjustment for potentially confounding variables, this association remained significant only in the high individualism tertile; a SD increase in wellbeing was associated with a 37% (HR = 0.63; 95% CI = 0.49-0.81) decrease in cardiovascular mortality risk. Further adjustment for potentially mediating variables only attenuated this association slightly: HR = 0.64; 95% CI = 0.50-0.84.

In addition to wellbeing, significant predictors of reduced cardiovascular mortality risk in the fully adjusted model in all three tertiles included: younger age and being female. Additional factors associated with a reduced risk in the low individualism tertile were no history of diabetes, living with a partner, engaging in vigorous or moderate physical activity and drinking twice a month or less (compared with drinking daily or almost daily). Additional factors in the moderate individualism tertile were not abstaining from alcohol (compared with drinking daily or almost daily) and being a non-smoker or former smoker. Finally, additional factors in the high individualism tertile were regular vigorous physical activity (compared with physical inactivity) and being a non-smoker (compared with being a current smoker).

Table 5.5

Hazard ratios (95% confidence intervals) for mortality from cardiovascular disease according to a SD increase in wellbeing score, n = 11,593 [a]

Model	**Individualism**	**Cases/N**	**HR (95% CI)**
Age and sex	Low	133/4340	0.84 (0.72-0.98)*
	Moderate	67/3431	0.75 (0.58-0.97)*
	High	74/3822	0.61 (0.50-0.76)**
Confounding variables [b]	Low		0.90 (0.75-1.08)
	Moderate		0.74 (0.55-1.01)
	High		0.63 (0.49-0.81)**
Confounding and mediating variables[c]	Low		0.95 (0.79-1.15)
	Moderate		0.81 (0.60-1.10)
	High		0.64 (0.50-0.84)**

[a] p for wellbeing score × individualism score interaction = 0.007

[b] Confounding variables = socioeconomic status, country level health care index score, level of education, depressive symptoms, marital status and history of chronic disease or any long term health problems.

[c] Mediating variables = health behaviours and BMI

* p <0.05, ** p <0.001

358 cancer related deaths were reported over the follow-up period. The association between wellbeing score and cancer mortality risk was not significant in the age- and sex-adjusted model (HR = 0.91; 95% CI = 0.82-1.00), the model adjusted for

confounding variables (HR = 0.95; 95% CI = 0.84-1.07) or the model adjusted for confounding and mediating variables (HR = 0.99; 95% CI = 0.88-1.12). The wellbeing × individualism interaction was also not significant ($p = 0.60$).

To test for possible bias due to missing data, we used multiple multivariate imputation to impute values of covariates with missing values. The pooled effect sizes from analysis with imputed information were similar to those obtained from analysis predicting risk of all-cause mortality employing the sample with complete data. These results therefore suggest that missing covariate data did not bias the results. See table 5.6 for a comparison of results.

Table 5.6

Hazard ratios (95% confidence intervals) for all-cause mortality according to a SD increase in wellbeing score from analysis with imputed missing covariates and from analysis with complete data

Model	**Imputed Covariates**	**Complete Data**
	HR (95%-CI)	**HR (95%-CI)**
Age and sex	0.76 (0.72-0.78)**	0.78 (0.74-0.82)**
Confounding and mediating variables[a]	0.92 (0.87-0.97)*	0.92 (0.86-0.97)*

[a] Confounding variables = socioeconomic status, country level health care index score, level of education, depressive symptoms, marital status and history of chronic disease or any long-term health problems. Mediating variables = health behaviours and BMI

* $p < 0.05$, ** $p < 0.001$

Discussion

We tested whether associations between wellbeing and self-rated health or mortality risk were consistent among people from individualistic and collectivistic cultures. Our results were mixed. In cross-sectional analysis, higher wellbeing was more strongly related to better self-rated health among people from individualistic cultures. In predicting all-cause mortality, however, we found that higher wellbeing was associated with a reduced risk, but individualism did not moderate this effect. Analysis of cause-specific mortality, on the other hand, revealed a significant association between higher wellbeing and reduced risk of mortality from cardiovascular disease, which was significantly stronger among participants in countries scoring high on individualism. Wellbeing was not associated with risk of cancer related mortality.

The stronger link between wellbeing and self-rated health or cardiovascular mortality in more individualistic countries, suggests that these associations differ between cultures. By comparing only European countries and controlling for differences in health care provision, SES, education and health behaviours, we were able to rule out the effect of multiple between country differences not directly related to the cultural dimension of individualism. The moderating effect of individualism observed in our study, is similar to the effect reported in previous cross-sectional studies into the association between negative affect and health across individualist and collectivist cultures. In these studies, there was stronger link between negative affect and number of chronic conditions or levels of interleukin-6 in American (individualistic)

compared with Japanese (collectivistic) samples (Curhan et al., 2014; Miyamoto et al., 2013).

Various mechanisms might explain why there is a stronger link between wellbeing and health in individualistic compared with collectivistic cultures. Firstly, as outlined in the Introduction, this effect may reflect the greater emphasis placed on wellbeing in individualistic cultures. High wellbeing may lead to more positive emotion in individualistic cultures as it is valued. This more positive evaluation may confer an additional health benefit. Furthermore, an emphasis on personal wellbeing in individualistic cultures, may cause individuals with low wellbeing to feel distressed, which in turn, may impact negatively on health.

Although numerous authors have reported that wellbeing is valued more highly in individualistic than collectivistic cultures (Ahuvia, 2002; Diener & Suh, 2000; Steptoe, Tsuda, et al., 2007; Veenhoven, 1999), others have argued that these findings reflect a failure to measure wellbeing in collectivistic cultures (Uchida, Norasakkunkit, & Kitayama, 2004). Wellbeing is commonly defined as a cognitive and affective appraisal of the quality of one's own life (Diener, 2000). Uchida, Norasakkunkit and Kitayama (2004) argue that this definition is valued equally across cultures; however, there are likely to be cultural differences regarding which factors an individual considers when appraising their quality of life. Norasakkunkit and Kalick (2002) point out that the majority of wellbeing measures currently used in psychological research assess factors that are prioritised in individualistic but not collectivistic cultures (e.g. autonomy, personal success). The CASP-12 (wellbeing measure) is a good example of this bias: participants rate the extent to which they

feel autonomous and have control over their lives. Although these are important correlates of wellbeing from an individualist perspective, they are unlikely to constitute 'a good life' in collectivistic cultures. Bearing this criticism in mind, the current results (stronger association between CASP-12 score and self-rated health or mortality risk from cardiovascular disease in individualist countries) could reflect a failure to capture wellbeing among participants from more collectivistic cultures.

Even if our measure of wellbeing was not culturally biased, cross-cultural differences in the determinants of wellbeing could account for the moderating effect of culture on the association between wellbeing and risk of cardiovascular disease mortality. Specifically, the stronger association in more individualistic countries could reflect the fact that wellbeing is more dependent on good physical health or health related variables in these cultures. In this sense, ratings of wellbeing could function as an index of physical health in these cultures and thus be more closely related to subsequent health outcomes. In support of this argument, in our study, wellbeing was more strongly related to self-rated health in more individualistic countries.

Although wellbeing was more strongly related to self-rated health and cardiovascular related mortality in individualistic cultures, the association between wellbeing and risk of all-cause mortality did not vary as a function of individualism. It is unclear why we found evidence of an interaction between wellbeing and level of individualism in analysis predicting mortality from cardiovascular disease but not from all causes. It is possible that the mechanisms which underlie the association between wellbeing and causes of death other than cardiovascular disease, are less

likely to vary as a function of individualism. However, further work is needed to confirm this effect.

Wellbeing score was not associated with cancer mortality risk. Previous findings regarding the association between wellbeing and cancer risk have been mixed. Some studies have documented a significant association between wellbeing and cancer in women (Feller et al., 2013; Wakai et al., 2007), but we failed to find any association between wellbeing and incident cancer in the ELSA sample (n = 7,474). Similarly, Lillberg et al. (2002) found no association between wellbeing and risk of breast cancer in a Finnish cohort.

Strengths of the study include the sample – which was large and designed to be representative of people aged 50 and older living in Europe. The available data allowed for adjustment for many potential confounder and mediator variables. However, several limitations should be noted. Firstly, over a third of the participants (37%) were excluded due to missing wellbeing data. Excluded participants differed to those included in our sample on a number of covariate variables. Thus, excluding these participants may have biased the results; however, analysis with imputed missing covariate and wellbeing data yielded similar effect sizes to those obtained for the sample with complete data, suggesting that this exclusion did not bias our results. Secondly, date and cause of death was obtained from interviews with a relative or friend of the participant rather than from official death records and may therefore be less reliable. Thirdly, a significant proportion of participants had missing mortality data. At wave 2, information on vital status could not be obtained for 19% of participants in our sample, by wave 5, 38% had missing vital status data. Schulz

and Doblhammer (2011) have shown that all-cause mortality in SHARE is underestimated. This is due to missing data on vital status at follow-up, as well as the fact that participants from the institutionalised population were not included in the sample (Schulz & Doblhammer, 2011). Additionally, it appears that the prevalence of mortality from cardiovascular disease was underestimated in our sample. According to Eurostat, the statistical office of the European Union, around 20% of deaths among Europeans aged 65 and over, are from cancer, and 40% are from cardiovascular disease ('Causes of death statistics - people over 65 - Statistics Explained,' 2017). Although the proportion of cancer related deaths in our sample (25%) is in line with the Eurostat report, the proportion of deaths from cardiovascular disease in our sample (20%) is substantially lower than the proportion reported by Eurostat. Because of these limitations, it is unclear whether our findings are generalisable. A replication of our study with a more valid measure of mortality is warranted. Finally, although we controlled for between-country differences in socio-economic status, education, some health behaviours and healthcare provision, it is possible that additional unmeasured differences between more and less individualistic countries (e.g. in diet or health literacy) may account for the apparent effect of individualism in our study.

It should be noted that, although Hofstede, Hofstede and Minkov's (2010) cultural dimensions are a popular tool in intercultural research, this approach has been criticised on a number of grounds. Firstly, some authors have questioned whether it is appropriate to treat nations as cultural entities, as there is a great deal of cultural variability within nations (e.g., McSweeney, 2002). In support of their approach,

Minkov and Hofstede (2014) have shown that people from different European regions can be grouped into national clusters based on measures of their values. A second common criticism of Hofstede's IBM study (Hofstede, 1984), on which the cultural dimensions are based, relates to the representativeness of the study sample. Hofstede argues that comparing samples of very similar people (i.e. working in the same positions in the same company) across countries, allowed him to isolate the effect of cultural differences. However, others have argued that Hofstede's findings may not generalise to other members of society, for instance, those who live in remote rural areas (Triandis, 1982). In support of Hofstede's findings, his dimensions have been largely replicated using a range of samples including employees of six international corporations (excluding IBM) in 32 countries (Shane, 1995), commercial airline pilots in 19 countries (Merritt, 2000), top municipal civil servants in 14 countries (Mouritzen & Svara, 2002), consumers in 15 European countries (De Mooij & Hofstede, 2002), and employees of an international bank in 19 countries (van Nimwegen, 2002).

We hope that our findings will inspire further investigation into the association between wellbeing and health across cultures. Researchers could test whether the previously documented association between wellbeing and incident cardiovascular disease (Boehm & Kubzansky, 2012) is also stronger in individualistic than in collectivistic cultures. Wellbeing scales oriented towards more collectivist values are now being developed (Datu, King, & Valdez, 2016). It would be interesting to test whether our finding of a stronger link between wellbeing and self-rated health or risk of mortality from cardiovascular disease in more individualist cultures would be

replicated if the CASP-12 was replaced with a more collectivist measure of wellbeing. It is possible that the opposite effect would be found – with stronger associations between 'collectivist wellbeing' and health in more collectivist cultures.

To conclude, although previous studies have documented cross-cultural difference in the association between negative affect and health (Curhan et al., 2014; Miyamoto et al., 2013), our findings regarding the link between wellbeing and health were mixed. We found no evidence of a moderating effect of individualism score in analysis predicting all-cause mortality. However, our results did provide some evidence that individualism moderates the association between wellbeing and self-rated health or risk of mortality from cardiovascular disease. Although prospective studies are needed to confirm our finding, our work illustrates the importance of incorporating cultural context into the study of wellbeing and health.

Chapter 6: The Interaction between Stress and Positive Affect in Predicting Mortality

Introduction

In chapter 5 we identified individualism/collectivism as a potential moderator of the association between wellbeing and longevity. In this chapter, we tested for the effect of another potential moderator of this association; namely, perceived stress.

Pressman and Cohen (2005) have proposed two potentially compatible models that might explain the positive association between positive affect and good health or longevity. Positive affect is a component of psychological wellbeing and can be defined as the experience of positive emotion such as happiness, joy, excitement, or contentment (Pressman & Cohen, 2005). According to the direct effects model, the experience of positive affect impacts directly on physiological processes and health behaviours associated with healthy functioning. The stress-buffering model, on the other hand, proposes that positive affect is associated with good health because it protects against the pathogenic consequences of psychological stress (Pressman & Cohen, 2005). If the positive association between positive affect and better health is caused by this stress buffering mechanism, then the protective effect of positive emotion should be stronger for people who experience more stress. In other words, psychological stress should moderate the association between positive affect and health. To date, researchers interested in the link between higher positive affect and lower mortality risk have focused on the direct effects model; consequently, it is unclear whether perceived stress moderates this risk association.

Positive affect can be measured at the trait or state level; trait measures assess how an individual 'typically' feels and state measures assess how an individual feels at a particular point in time. Both trait and state measures of positive affect have been linked to longevity (Y. Zhang & Han, 2016) and biomarkers of neuroendocrine, inflammatory and cardiovascular functioning (Pressman & Cohen, 2005; Steptoe, Gibson, et al., 2007; Steptoe, O'Donnell, Badrick, et al., 2008).

The idea that positive affect serves an adaptive function during periods of stress was prompted by the observation that stress and positive affect can co-occur (Folkman & Moskowitz, 2000). For example, in a longitudinal study of 253 male caregivers, participants reported experiencing positive affect as frequently as they did negative affect (Folkman, 1997). Accounts of positive affect during periods of severe stress can also be found in studies into the process of bereavement (Tweed & Tweed, 2011; Wortman & Silver, 1987), and the onset of disability (Wortman & Silver, 1987).

Pressman and Cohen (2005), hypothesize that the experience of positive affect during periods of stress could reduce behavioural and physiological stress responses. Health harming responses to stress include overactivation of allostatic systems, such as the hypothalamic–pituitary–adrenal (HPA) axis or the autonomic nervous system (ANS) (Juster, McEwen, & Lupien, 2010), and an increase in unhealthy behaviours such as smoking, alcohol consumption, or substance abuse (Schneiderman, Ironson, & Siegel, 2005). The stress buffering model identifies physiological and psychosocial factors associated with positive affect that may interact with these stress responses (Pressman & Cohen, 2005). Firstly, at a physiological level, the release of endogenous opioids (a correlate of high positive affect) could dampen HPA and ANS

responses to stress (Drolet et al., 2001; Smith & Baum, 2003). At a cognitive level, positive affect may facilitate creative problem solving or the appraisal of a stressful situation as an opportunity or challenge (Ashby, Isen, & others, 1999; Salovey, Rothman, Detweiler, & Steward, 2000). These responses may reduce exposure to stressors, and, consequently, both HPA and ANS activity, as well as health harming behaviours. Finally, Pressman and Cohen (2005) suggest that individuals who experience more positive affect are more likely to have social and physical resources that facilitate adaptive coping – both at a behavioural and physiological level. Similar mechanisms are proposed in Fredrickson's Broaden-and-Build theory (Fredrickson, 2001; Fredrickson et al., 2000), which posits that the experience of positive affect can help individuals build the psychosocial resources needed to cope with stress and adversity. Fredrickson (2001) also proposes that the experience of positive emotions following a stressful experience can help undo the physiological responses (specifically cardiovascular reactivity) and cognitive responses (narrowing of the thought-action repertoire) to stress (Fredrickson, 2001).

Studies of positive affect and stress responses provide evidence for the mechanisms identified in the stress-buffering model and the Broaden-and-Build theory. Several studies have tested whether positive affect dampens physiological responses to laboratory stress tasks. Fredrickson, Mancuso, Branigan, and Tugade (2000) measured cardiovascular recovery following a stress induction task in 170 students. Participants who viewed films that elicited amusement or contentment following the stress task were characterized by quicker cardiovascular recovery than participants who viewed neutral films or films that elicited sadness. Similarly, in 170 participants,

Kraft and Pressman (2012) found that maintaining a positive (versus neutral) facial expression during a stress task was associated with lower heart rate during the stress recovery period. Finally, in 72 healthy men, frequency of self-reported positive affect was associated with lower systolic blood pressure during a stress task and quicker diastolic pressure recovery following the task (Steptoe, Gibson, et al., 2007). Although less is known regarding associations between stress, positive affect, and health behaviours, there is evidence that greater wellbeing is associated with positive behaviour change following stressful events, such as diagnosis of chronic disease (Chaves & Park, 2015; Hawkins et al., 2010; Park et al., 2008). In addition, in a longitudinal study of 83 college students, positive affect was associated with better sleep efficiency (hours of sleep/time in bed) on days of higher stress but not on days of lower stress (Pressman, Jenkins, Kraft-Feil, Rasmussen, & Scheier, 2017).

Fewer studies have tested the key prediction from these theories, that is, there should be an interaction between positive affect and perceived stress in predicting health outcomes. In a cross-sectional study of 382 participants, the association between higher stress and lower self-rated health was significantly moderated by positive affect such that the association was strongest at low levels of positive affect (Bränström, 2013). Blevins, Sagui, and Bennett (2016) tested whether self-reported stress moderated the association between higher positive affect and lower levels of systemic inflammation. Using cross-sectional data from the National Longitudinal Study of Adolescent to Adult Health (n = 3,093), they found that higher positive affect was associated with lower levels of inflammation only among participants who reported higher levels of stress. Finally, in an experimental study (n = 60), Robles,

Brooks, and Pressman (2009) compared the strength of the association between positive affect and skin barrier recovery (following a 'tape stripping' procedure) between participants assigned to a stress condition and participants assigned to a control condition. Higher positive affect was associated with faster recovery in the stress condition but not in the control condition.

In a recent meta-analysis on positive affect as a predictor of longevity, Zhang and Han (2016) identified one study that tested for an interaction between perceived stress and positive affect. This study used data from the National Health and Nutrition Examination Study I (NHANES I) Epidemiologic Follow-Up Study (NHEFS) (Moskowitz, Epel, & Acree, 2008). The authors found evidence of a stress-buffering effect only in a subsample of participants who had no chronic conditions and were over the age of 65. In this subsample, the association between higher positive affect and lower mortality risk was strongest among participants who reported higher stress. However, as the primary aim of Moskowitz and colleagues' (2008) study was to compare participants with and without diabetes, the sample was restricted to participants diagnosed with diabetes (n = 715) and participants without any chronic conditions (n = 2,673).

In summary, previous studies report that positive affect protects against some health harming responses to stress and that positive associations between positive affect and better health are stronger under conditions of high stress. However, it is unclear whether this moderating effect applies to the association between higher positive affect and lower mortality risk. The aim of the current study was to test whether

perceived stress moderated the positive association between positive affect and longevity in a large, nationally representative sample.

Methods

Study Population

We used data from the NHEFS (Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS), 2012). The NHANES I (1971-1975) data were taken from a nationwide probability sample of 32,000 Americans aged 1 to 74. The NHEFS began in 1982 and included 12,220 participants aged 25-74 who had completed the medical examination in NHANES I. Subsequent waves of NHEFS data collection were conducted in 1986, 1987, and 1992.

Positive affect, stress, and covariate measures, apart from wealth and height, were taken from the NHEFS wave 1 (1982) interview. Wealth and height were taken from the NHANES I (1971-1975) interview.

Positive affect

As has been done previously (Cornoni-Huntley, Huntley, & Feldman, 1990; Costa et al., 1987), positive affect was measured using the positive affect subscale of the General Wellbeing Questionnaire (GWQ) (Fazio, 1977). The positive affect subscale consists of three questions: ‘How have you been feeling in general in the past month?’ (anchors were ‘in excellent spirits’ and ‘in very low spirits’), ‘How happy, satisfied, or pleased have you been with your personal life, during the past month?’, and ‘How much energy, pep, vitality have you felt, during the past month?’. This

subscale's scores range from 0 to 20 with higher scores indicating higher positive affect. Cronbach's alpha for this scale in our sample was 0.60.

Stress

Following Moskowitz et al. (2008), we used three items from the GWQ as a measure of perceived stress. The items were: 'Have you been under or felt you were under any strain, stress, or pressure during the past month?', 'Have you been anxious, worried or upset, during the past month?', and 'How relaxed or tense have you been during the past month?' Scores ranged from 1 to 22 with higher scores indicating higher levels of perceived stress. Cronbach's alpha for this scale in our sample was 0.75. There is no clear agreement on the definition of perceived stress in the literature (Stults-Kolehmainen & Sinha, 2014); however, the stress items used in our study are comparable to a subset of those used for the stress scale of the Depression Anxiety Stress Scales (DASS) (Clara, Cox, & Enns, 2001; Norton, 2007), a popular measure of subjective stress. Similar DASS items include: 'I found it difficult to relax', 'I found it hard to wind down', 'I was in a state of nervous tension', and 'I found myself getting upset rather easily'. The DASS defines depressive symptoms in terms of low mood, motivation, and self-esteem and stress in terms of tension, nervousness and irritability (Clara et al., 2001; Norton, 2007).

Mortality

Participants' vital status was recorded until the end of 1992. Information regarding date and cause of death was obtained from death certificates.

Covariates

We adjusted for variables that might confound or mediate the association between positive affect and mortality risk. These included age, sex, race/ethnicity, socio-economic status, level of education, depressive symptoms, marital status, physical activity, smoking status, fruit and vegetable consumption, alcohol consumption, body mass index (BMI), sleep duration, and history of cancer, cardiovascular disease, and chronic lung disease. These factors have previously been associated with mortality risk (Beydoun et al., 2016; Case & Paxson, 2005; Ford et al., 2011; Gallicchio & Kalesan, 2009; Grandner & Patel, 2009; Johnson et al., 2000; Kesteloot & Huang, 2003; Krieger et al., 1997; Majer et al., 2011; Prospective Studies Collaboration, 2009; Riley & Cowan, 2014; Saz & Dewey, 2001; Sorlie et al., 1995; Wang et al., 2014) as well as positive affect or wellbeing (Brett et al., 2012; Grandner & Patel, 2009; Hanmer et al., 2006; Martin Pinquart & Sörensen, 2000; Pressman & Cohen, 2005; Rippe et al., 1998; Sjöström et al., 1992; Steptoe et al., 2014; Wikman et al., 2011; Woody & Green, 2001).

Wealth was indexed by family income from all sources over the past 12 months. We chose to use the family income measure from the NHANES 1 (1971-1975) interview rather than NHEFS (1982) interview as the latter had a larger amount of missing data (n = 828). Family income measures from NHANES 1 and NHEFS were strongly correlated (r = 0.66). Responses to the family income question in NHANES 1 were recorded as either less than $1,000, a specific quantity between $1,000 and $25,000, or $25,000 or more. We grouped participants into four income categories: <$3,000, $3,000-$5,999, $6,000-14,999 and >$14,999. Education was measured as the highest

year of regular school (including college) attended. Based on their responses, we grouped participants into 4 categories: ≤ 8 years of education, 9-11 years, 12 years, and > 12 years. Based on the information available, participants' race/ethnicity was categorised as 'black', 'other', or 'white'. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The CES-D consists of twenty items and is designed to measure symptoms of depression in the general population. The CES-D score was treated as a continuous variable. Participants reported whether they were married, divorced, widowed, or never married. We used these responses to create two categories: 'married' or 'not married'. Participants were asked to report the amount of physical activity they engaged in during recreational activities and during a typical day (excluding recreational physical activity). Response options were 'much exercise', 'moderate exercise', and 'little or no exercise'. As responses to these two questions about physical activity were distributed differently, we created two separate variables: recreational physical activity and non-recreational physical activity. Participants were asked whether they had ever smoked more than 100 cigarettes and whether they were a current smoker. Based on response to these two questions, participants were classified as non-smokers, former smokers, and current smokers. Participants were asked to estimate the number of servings of fruit and vegetables they had per day. We dichotomized responses based on number of servings – either 5 or more servings per day or less than 5 servings per day. Participants were asked to describe their drinking habits using the response options 'abstainer', 'light drinker', 'moderate drinker', and 'heavy drinker'. As only 69 participants identified themselves as heavy drinkers, we grouped heavy and moderate drinkers in the same category. Participants

were asked to estimate the average number of hours they slept each night. As has been done previously (Gangwisch, Malaspina, Boden-Albala, & Heymsfield, 2005), we categorized sleep duration as 4 hours or fewer, between 5 and 9 hours, and 10 or more hours. Although participants' weight was measured in 1982, height measures were only taken for NHANES I (1971-1975). We thus computed participant BMI from these two measures and treated BMI as a continuous variable. The correlation between the 1971-1975 height and weight measures (r = 0.47, p <0.001) was not significantly different from the correlation between the 1971-1975 height measure and the 1982 weight measure (r = 0.48, p <0.001) (z = 1.46, p = 0.07). Finally, participants were asked if a doctor had ever diagnosed them with cancer (breast cancer, skin cancer, or any other type of cancer), cardiovascular disease (CVD) (stroke or heart attack), or chronic lung disease (chronic bronchitis or emphysema).

Analytical Sample

Of the 12,220 participants in the NHEFS sample, we excluded 1,697 participants due to missing vital status data and an additional 1,981 participants due to missing covariate data. This left us with an analytic sample of 8,542 participants. Missing covariate data ranged from 0.2% for marital status to 9% for depression. The excluded participants differed from the analytic sample on several variables (see table 6.1 for a summary of these differences).

Table 6.1

Baseline characteristics of participants included in and excluded from the analytic sample

Characteristic	**Included**	**Excluded**	**N**[a]	***p*-trend**[b]
Positive affect score, *M* (SD)	13 (4)	12 (4)	9,974	<0.001
CES-D score, *Mdn* (IQR)	8 (2-12)	10 (3-14)	9,512	<0.001
Stress score, *M* (SD)	8 (4)	8 (5)	9,969	0.001
Age, *M* (SD)	55.89 (14)	62.14 (15)	10,523	<0.001
BMI, (kg/m2) *M* (SD)	26.30 (4.97)	26.03 (5.11)	9,972	0.066
Female, No. (%)	5371 (63)	1907 (52)	12,220	<0.001
Race/Ethnicity No. (%)			12,220	<0.001
Black	1032 (12)	670 (18)		
White	7425 (87)	2974 (81)		
Other	85 (1)	34 (1)		
Married, No. (%)	5953 (70)	2110 (58)	12,181	<0.001
Wealth category, $ (%)			11,789	<0.001
<3,000	887 (10)	809 (25)		
3,000-5,999	1385 (16)	753 (23)		
6,000-14,999	4246 (50)	1240 (38)		
>14,999	2024 (24)	445 (14)		
Education category, No. (%)			12,146	<0.001
≤8 years	1761 (21)	1501 (42)		

9-11 years	1403 (16)	634 (18)		
12 years	3188 (37)	872 (24)		
>12 years	2190 (26)	597 (17)		
Recreational activity, No. (%)			10,063	<0.001
Inactive	2915 (34)	657 (43)		
Moderate	4248 (50)	651 (43)		
Vigorous	1379 (16)	213 (14)		
Non-recreational, No. (%)			10,063	<0.001
Inactive	1395 (16)	337 (22)		
Moderate	4792 (56)	796 (52)		
Vigorous	2355 (28)	385 (25)		
Alcohol consumption, No. (%)			12,170	<0.001
Abstainer	3688 (43)	2712 (75)		
Light drinker	3890 (46)	730 (20)		
Moderate drinker	964 (11)	186 (5)		
Smoking status, No. (%)			11,185	<0.001
Non smoker	3873 (45)	1609 (61)		
Former smoker	2287 (27)	538 (20)		
Smoker	2382 (28)	496 (19)		
≥ 5 fruit and vegetables, No. (%)	3162 (37)	663 (38)	10,298	0.577
Sleep categories, No. (%)			9,789	<0.001
<5 hours	206 (2)	65 (5)		
5-9 hours	8076 (95)	1107 (89)		

>9 hours	260 (3)	75 (6)		
History of CVD, No. (%)	507 (6)	924 (28)	11,833	<0.001
History of cancer, No. (%)	749 (9)	714 (20)	12,154	<0.001
History of lung disease, No. (%)	860 (10)	516 (14)	12,171	<0.001

[a] Number of participants with data.

[b] Statistical significance is based on $\chi 2$ tests or t-tests, as appropriate.

Statistical analysis

Analyses were performed in RStudio 1.0.143 (RStudio Team, 2016). Cox's proportional hazard regressions were used to examine the association between positive affect and perceived stress at baseline and mortality over the follow-up period. Survival time in days was calculated from the date of the first NHEFS interview to the date of death or, for participants who did not die during the follow up, the date of their last interview.

We adjusted for covariates in three stages. Model 1 was adjusted for age and sex. Model 2 was additionally adjusted for potentially confounding variables: demographic variables (race/ethnicity, wealth, education, marital status), history of chronic conditions (cancer, CVD or respiratory disease), and depressive symptoms. Model 3 was further adjusted for potentially mediating variables: health behaviours (smoking status, alcohol consumption, physical activity, and diet), sleep duration, and BMI. We tested whether the association between positive affect and mortality risk varied per level of stress by including a stress score × positive affect score interaction term in each of the three models.

We calculated the impact of adjusting for health behaviours or wealth and education on the HR for the interaction between positive affect and perceived stress. We achieved this using the formula ([HR adjusted for age and sex – 1] – [HR adjusted for age, sex and covariate – 1]/[HR adjusted for age and sex– 1]) × 100 (Batty, Der, Macintyre, & Deary, 2006).

To test for possible bias due to missing data, we used multiple multivariate imputation to impute values of covariates with missing values using IBM SPSS Statistics 24 software. The imputation models included survival time, mortality, perceived stress, positive affect and the covariate variables. We generated 35 imputed datasets using chained equations imputation. The sample size for analysis with imputed data was 10,523.

Results

Table 6.2 shows the baseline characteristics of the sample (n = 8,542) according to positive affect tertile. On average, participants with higher positive affect were more likely to be male, younger, and married. These participants also tended to be wealthier, better educated, and engaged in more recreational and non-recreational physical activities, and had fewer depressive symptoms, lower perceived stress, and a lower BMI. Finally, on average, participants with higher positive affect consumed more alcohol, ate more fruit and vegetables, were less likely to sleep <5 hours or >9 hours a night, and were less likely to report a history of chronic disease. Table 6.3 shows correlations among positive affect, perceived stress, and the other baseline characteristics. The correlation between positive affect and perceived stress score was r = -0.51 (p<0.001).

Over the 10-year follow-up period, 1,507 deaths were reported. Table 6.4 shows bivariate associations between positive affect, perceived stress or covariate variables, and mortality risk.

Table 6.2

Baseline characteristics stratified according to tertiles of positive affect score (low, moderate and high positive affect)[a] *total n = 8,542*

Characteristics	**Low**	**Moderate**	**High**	***p*-trend**[b]
Age, *M* (SD)	57.85 (14.97)	55.66 (14.32)	53.68 (13.64)	<0.001
Female, No. (%)	2095 (69)	1977 (64)	1299 (54)	<0.001
Race/Ethnicity, No. (%)				0.46
Black	389 (13)	361 (12)	282 (12)	
White	2643 (87)	2713 (87)	2069 (87)	
Other	20 (1)	28 (1)	37 (2)	
Married, No. (%)	1936 (63)	2208 (71)	1809 (76)	<0.001
Wealth category, No. $ (%)[c]				<0.001
<3,000	438 (14)	275 (9)	174 (7)	
3,000-5,999	584 (19)	483 (16)	318 (13)	
6,000-14,999	1504 (49)	1570 (51)	1172 (49)	
>14,999	526 (17)	774 (25)	724 (30)	
Education category, No. (%)				<0.001
≤8 years	767 (25)	590 (19)	404 (17)	
9-11 years	575 (19)	488 (16)	340 (14)	
12 years	1099 (36)	1211 (39)	878 (37)	
>12 years	611 (20)	813 (26)	766 (32)	
CES-D score, *Mdn* (IQR)	12 (6-18)	5 (2-10)	3 (0-6)	<0.001

Stress score, *M* (SD)	10.26 (4.68)	7.55 (3.90)	5.33 (3.35)	<0.001
BMI, (kg/m2) *M* (SD)	26.50 (5.38)	26.36 (4.95)	25.93 (4.38)	<0.001
Recreational, No. (%)				<0.001
Inactive	1443 (47)	975 (31)	497 (21)	
Moderate	1336 (44)	1652 (53)	1260 (53)	
Vigorous	273 (9)	475 (15)	631 (26)	
Non-recreational, No. (%)				
Inactive	786 (26)	408 (13)	201 (08)	
Moderate	1746 (57)	1841 (59)	1205 (50)	
Vigorous	520 (17)	853 (27)	982 (41)	
Alcohol, No. (%)				<0.001
Abstainer	1498 (49)	1304 (42)	886 (37)	
Light drinker	1249 (41)	1419 (46)	1222 (51)	
Moderate drinker	305 (10)	379 (12)	280 (12)	
Smoking status, No. (%)				0.64
Non-smoker	1370 (45)	1447 (47)	1056 (44)	
Former smoker	792 (26)	826 (27)	669 (28)	
Smoker	890 (29)	829 (27)	663 (28)	
≥ 5 servings fruit/veg, No. (%)	1049 (34)	1191 (38)	922 (39)	0.001
Sleep duration, No. (%)				<0.001
<5 hours	125 (4)	51 (2)	30 (1)	
5-9 hours	2810 (92)	2959 (95)	2307 (97)	

>9 hours	117 (4)	92 (3)	51 (2)	
History of CVD, No. (%)	274 (9)	161 (5)	72 (3)	<0.001
History of cancer, No. (%)	309 (10)	258 (8)	182 (8)	0.003
History of lung disease, No. (%)	443 (15)	282 (9)	135 (6)	<0.001

[a] The cut points for positive affect tertiles were based on the analytic sample.

[b] Statistical significance is based χ^2 tests or one-way ANOVA, as appropriate.

[c] $3,000 in 1975 has the equivalent value of $13,646 in 2017.

Table 6.3

Correlations among predictor and covariate variables

Variable	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
1 Stress	-	.56	-.51	-.20	.00	-.14	.00	.03	.08	-.11	.03	.04	.00	-.09	.04	-.02	.08
2 CES-D		-	-.54	.05	.03	-.11	-.14	-.16	-.17	-.17	-.08	.02	-.07	-.07	.08	.02	.09
3 Positive affect			-	-.12	-.04	.11	.13	.17	.14	.29	.09	-.01	.05	.04	-.12	-.04	-.14
4 Age				-	-.04	.09	-.22	-.30	-.35	-.14	-.23	-.19	.04	.07	.19	.19	.09
5 BMI					-	.02	.00	-.05	-.09	-.13	-.07	-.09	-.01	-.03	.00	-.03	-.03
6 Sex						-	.02	.09	-.01	.11	.20	.17	-.10	.03	.09	.00	.01
7 Married							-	.35	.17	.09	.08	.02	.05	-.01	-.02	-.03	-.04
8 Wealth								-	.46	.12	.26	.08	.06	-.01	-.09	-.04	-.06
9 Education									-	.12	.26	.01	.09	-.02	-.12	-.03	-.09
10 Exercise										-	.10	.03	.03	-.01	-.10	-.03	-.07
11 Alcohol											-	.29	-.07	-.01	-.06	-.04	-.03
12 Smoking												-	-.11	-.01	.02	-.03	.11
13 Diet													-	.02	.01	.01	-.01
14 Sleep														-	.00	.03	-.01
15 History of CVD															-	.04	.08
16 History of cancer																-	.04
17 History of lung disease																	-

Higher scores = better diet, more years education, more exercise, greater alcohol consumption, being female, being married and having a history of chronic disease. Smoking coded as: current = 3, former = 2, non-smoker = 1.

Table 6.4

Bivariate associations for positive affect, stress and covariate variables with mortality risk

Variable	**HR (95% CI)**	***p***
Positive affect	0.73 (0.69-0.76)	<0.001
CES-D	1.02 (1.02-1.03)	<0.001
Stress	0.83 (0.78-0.87)	<0.001
Age	1.10 (1.09-1.10)	<0.001
BMI	0.97 (0.96-0.98)	<0.001
Sex: male vs. female	1.91 (1.72-2.11)	<0.001
Race/Ethnicity		
Black vs. white	1.22 (1.05-1.41)	0.008
Other ethnicity vs. white	0.90 (0.52-1.56)	0.72
Wealth $		
3,000-5,999 vs. <3,000	0.67 (0.58-0.78)	<0.001
6,000-14,999 vs. <3,000	0.33 (0.28-0.37)	<0.001
>14,999 vs. <3,000	0.21 (0.17-0.25)	<0.001
Education		
9-11 years vs. ≤8 years	0.44 (0.38-0.51)	<0.001
12 years vs. ≤8 years	0.25 (0.22-0.29)	<0.001
>12 years vs. ≤8 years	0.26 (0.23-0.30)	<0.001
Recreational activity		
Moderate vs. inactive	0.56 (0.51-0.63)	<0.001
Vigorous vs. inactive	0.41 (0.35-0.49)	<0.001
Non-recreational activity		

Moderate vs. inactive	0.50 (0.45-0.57)	<0.001
Vigorous vs. inactive	0.32 (0.28-0.38)	<0.001
Alcohol consumption		
Light drinker vs. abstainer	0.58 (0.52-0.65)	<0.001
Moderate drinker vs. abstainer	0.57 (0.47-0.68)	<0.001
Smoking status		
Former smoker vs. non-smoker	1.31 (1.17-1.48)	<0.001
Smoker vs. non-smoker	0.89 (0.79-1.02)	0.086
Diet: ≥ 5 fruit and vegetables vs. < 5	0.87 (0.78-0.97)	0.012
Sleep duration		
5-9 hours vs. <5 hours	0.58 (0.44-0.76)	<0.001
>9 hours vs. <5 hours	1.58 (1.14-2.19)	0.006
History of CVD vs. no history	4.02 (3.51-4.61)	<0.001
History of cancer vs. no history	2.60 (2.28-2.97)	<0.001
History of chronic lung disease vs. no history	2.05 (1.79-2.34)	<0.001

In a model adjusted for age, sex, perceived stress, and positive affect, positive affect was associated with lower mortality risk (hazard ratio [HR] per SD increase in positive affect score: 0.79; 95% confidence interval [CI]: 0.74-0.84) and stress was not associated with mortality risk (HR: 0.97; 95% CI: 0.91-1.03). We re-ran this model additionally including the interaction effect between positive affect and perceived stress. The interaction between positive affect and perceived stress was significant in the age- and sex-adjusted model (p<0.001) and remained significant following adjustment for demographic variables, history of chronic disease and

depressive symptoms (model 2) (p = 0.02), and health behaviours, and BMI (model 3) (p = 0.04). Table 6.5 displays the results of this fully adjusted model.

Table 6.5

HRs (95% CI) for all-cause mortality for variables in the fully adjusted model testing for a positive affect × stress interaction

Variable	**HR (95% CI)**	***p***
Positive affect	0.91 (0.85-0.97)	0.005
CES-D	1.00 (1.00-1.01)	0.24
Stress	0.90 (0.84-0.97)	0.008
Age	1.09 (1.08-1.09)	<0.001
BMI	0.99 (0.98-1.00)	0.041
Sex: male vs. female	1.82 (1.61-2.07)	<0.001
Marital status: married vs. single	0.77 (0.69- 0.87)	<0.001
Race/Ethnicity		
Black vs. white	1.11 (0.95-1.30)	0.19
Other ethnicity vs, white	1.15 (0.66-2.00)	0.61
Wealth $		
3,000-5,999 vs. <3,000	0.96 (0.83-1.12)	0.61
6,000-14,999 vs. <3,000	1.01 (0.87-1.18)	0.89
>14,999 vs. <3,000	0.90 (0.72-1.11)	0.31
Education		
9-11 years vs. ≤8 years	0.97 (0.83-1.13)	0.69
12 years vs. ≤8 years	0.87 (0.75-1.00)	0.052

>12 years vs. ≤8 years	0.80 (0.68-0.95)	0.013
Recreational activity		
Moderate vs. inactive	0.87 (0.77-0.99)	0.031
Vigorous vs. inactive	0.75 (0.61-0.91)	0.003
Non-recreational activity		
Moderate vs. inactive	0.75 (0.65-0.86)	<0.001
Vigorous vs. inactive	0.67 (0.56-0.80)	<0.001
Alcohol consumption		
Light drinker vs. abstainer	0.90 (0.80-1.012)	0.074
Moderate drinker vs. abstainer	1.06 (0.86-1.30)	0.60
Smoking status		
Former smoker vs. non-smoker	1.23 (1.08-1.40)	0.001
Smoker vs. non-smoker	1.65 (1.42-1.92)	<0.001
Diet: ≥ 5 fruit and vegetables vs. < 5	0.98 (0.88-1.09)	0.71
Sleep duration		
5-9 hours vs. <5 hours	0.86 (0.65-1.14)	0.30
>9 hours vs. <5 hours	0.96 (0.68-1.34)	0.79
History of CVD vs. no history	1.75 (1.52-2.02)	<0.001
History of cancer vs. no history	1.52 (1.33-1.74)	<0.001
History of chronic lung disease vs. no history	1.27 (1.10-1.46)	0.001
Positive affect × stress	1.04 (1.00-1.09)	0.036

To facilitate interpretation of the interaction effect, we divided the sample into tertiles according to perceived stress (low, moderate, and high), and conducted an analysis for each group separately. In the age- and sex-adjusted model, higher positive affect was associated with a lower mortality risk in all three groups. However, a stronger effect was observed in the higher perceived stress groups; a standard deviation (SD) increase in positive affect score was associated with a 13% reduction in mortality risk (HR: 87; 95% CI: 0.80-0.94) in the low perceived stress group, a 24% (HR: 0.76; 95% CI: 0.67-0.86) reduction in the moderate perceived stress group, and a 31% (HR: 0.69; 95% CI: 0.63-0.76) reduction in the high perceived stress group.

In model 2, the association between positive affect and mortality risk remained significant, although it was attenuated for all three groups. Again, a stronger effect was observed in the group with the highest levels of perceived stress; HRs for low, moderate, and high perceived stress groups per SD increase in positive affect score were 0.90 (95% CI: 0.82-0.98), 0.82 (95% CI: 0.72-0.93), and 0.77 (95% CI: 0.68-0.86), respectively. In the fully adjusted model (model 3), the association between positive affect and mortality risk was significant in the moderate (HR: 0.85; 95% CI: 0.74-0.97) and high (0.84; 95% CI: 0.75-0.95) perceived stress groups, but not in the low perceived stress group (HR: 0.98; 95% CI: 0.89-1.08). Table 6.6 displays HRs for all-cause mortality for each SD increase in positive affect.

Table 6.6

HRs (95% CIs) for all-cause mortality according to a SD increase in positive affect score divided by tertiles of perceived stress score

	Cases/N	**Model 1**	**Model 2**	**Model 3**
Low stress	665/2996	0.87 (0.80-0.94)**	0.90 (0.82-0.98)*	0.98 (0.89-1.08)
Moderate	452/2807	0.76 (0.67-0.86)**	0.82 (0.72-0.93)**	0.85 (0.74-0.97)*
High stress	390/2739	0.69 (0.63-0.76)**	0.77 (0.68-0.86)**	0.84 (0.75-0.95)*

Model 1 is adjusted for age and sex. Model 2 is further adjusted for demographic factors, history of chronic disease and depressive symptoms. Model 3 is additionally adjusted for health behaviours, sleep duration and BMI. ** p <0.001 * p <0.05

Figure 6.1 displays survival probabilities for the low, moderate, and high perceived stress groups stratified by tertile of positive affect. It should be noted that the association between perceived stress group and mortality risk was different from the association between perceived stress score (which was treated as a continuous variable) and mortality risk. Following adjustment for age, sex and positive affect tertile, participants in the moderate stress group had a lower mortality risk than participants in the low stress group. Mortality risk for participants in the low and high stress groups were not significantly different.

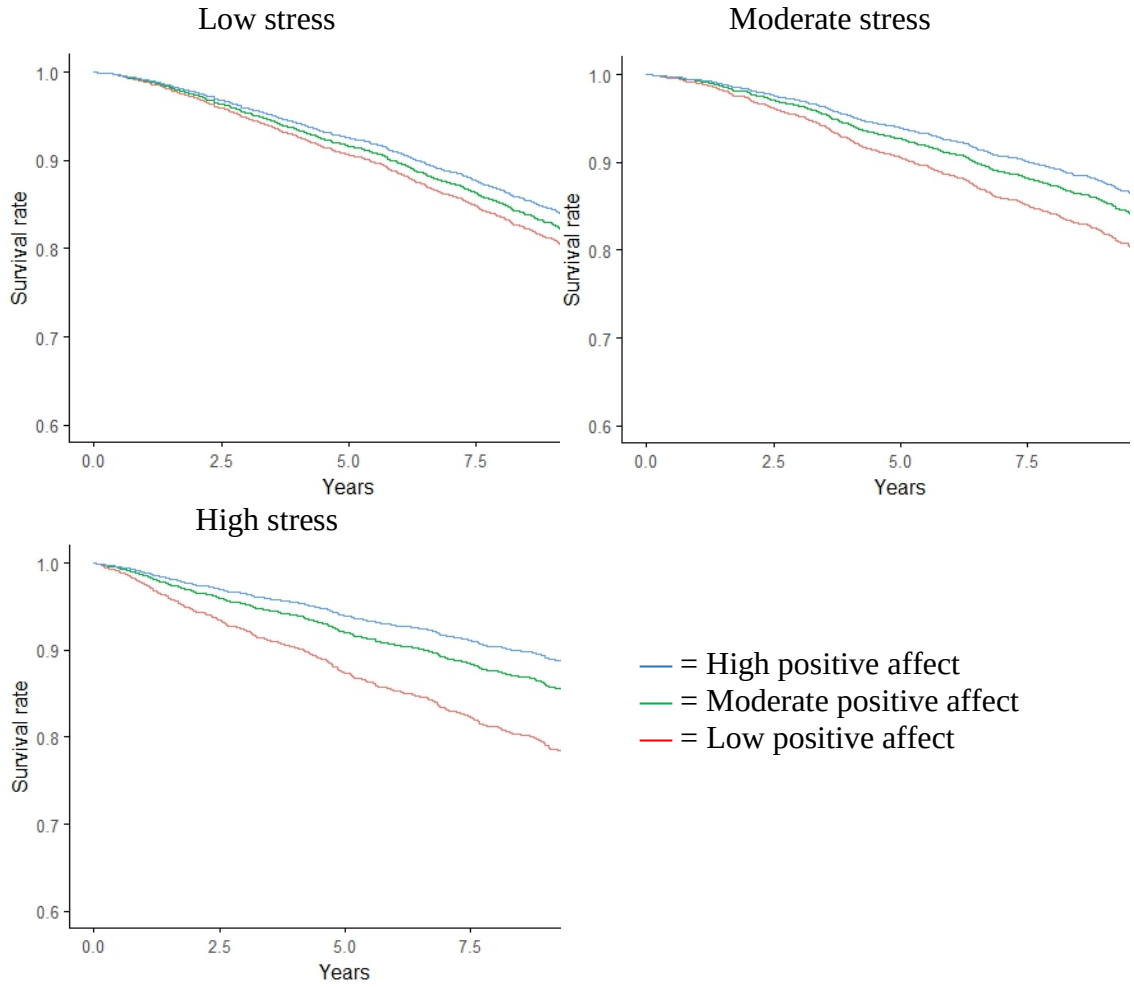

Figure 6.1

Survival probabilities (adjusted for age and sex) for the low, moderate and high stress groups stratified by tertile of positive affect

The pooled effect sizes from analysis with imputed information were largely similar to those obtained from analysis with complete data; however, the HR for mortality risk in the high stress group, was slightly higher in analysis with imputed data. See table 6.7 for a comparison of results. In analysis with imputed data, the interaction between positive affect and stress in predicting mortality risk was significant in the

age- and sex-adjusted model (p = 0.012), but not in the fully adjusted model (p = 0.331).

Table 6.7

Hazard ratios (95% confidence intervals) for mortality risk according to a SD increase in positive affect score from analysis with imputed missing covariates and from analysis with complete data

	Analysis	**Model 1**	**Model 3**
Low stress	Complete	0.87 (0.80-0.94)**	0.98 (0.89-1.08)
	Imputed	0.85 (0.79-.92)**	0.97 (0.89-1.05)
Moderate	Complete	0.76 (0.67-0.86)**	0.85 (0.74-0.97)*
	Imputed	0.74 (0.66-0.82)**	0.85 (0.76-0.96)*
High stress	Complete	0.69 (0.63-0.76)**	0.84 (0.75-0.95)*
	Imputed	0.71 (0.66-0.78)**	0.86 (0.77-0.95)*

Model 1 is adjusted for age and sex. Model 3 is additionally adjusted for demographic factors, history of chronic disease, depressive symptoms, health behaviours, sleep duration and BMI.

** p <0.001 * p <0.05

Additional analysis

We ran additional analysis to examine the association between stress and mortality risk. Following adjustment for age and sex, higher perceived stress was associated with a higher mortality risk (HR: 1.10; 95% CI: 1.04-1.16). This association was not significant following additional adjustment for demographic differences, depressive symptoms, history of chronic disease, and health behaviours (HR: 0.95; 95% CI: 0.89-1.02). However, when we additionally adjusted for positive affect, the association between stress and mortality risk became inverse and significant (HR: 0.93; 95% CI: 0.86-1.00). This inverse association was still significant after we included the interaction between perceived stress and positive affect. See table 6.5 for the results of this fully adjusted model.

We calculated the impact of adjusting for health behaviours or wealth and education on the HR for the interaction between positive affect and perceived stress. Adjusting for health behaviours attenuated the HR by 19%, adjusting for wealth and education attenuated the HR by 11%. We additionally tested if the interaction between perceived stress and positive affect varied as a function of wealth or education by including a three-way interaction term between perceived stress, positive affect and wealth or education. These three-way interaction effects were not significant (p = 0.42 for wealth, p = 0.73 for education).

The positive affect measure had a relatively low alpha ($\alpha = 0.60$). This was improved by excluding the vitality item ('How much energy, pep, vitality have you felt during the past month?') ($\alpha = 0.71$). In addition, there is evidence that the subdomain of energy or vitality may underlie positive associations between positive affect and

longevity (Pressman & Cohen, 2005). To examine the effect of the vitality item, we re-ran the analysis after excluding this item from the positive affect measure. The interaction between perceived stress and positive affect was significant in the age- and sex-adjusted model ($p = 0.001$) and in the model additionally adjusted for demographic differences ($p = 0.045$), but not in the fully adjusted model ($p = 0.059$). Positive affect was not associated with mortality risk in any of the perceived stress tertiles in the fully adjusted model. See table 6.7 for a summary of these results.

Table 6.8

HRs (95% CIs) for all-cause mortality according to a SD increase in positive affect score with and without the vitality item

Model	**Stress tertile**	**With vitality item**	**Without vitality item**
Model 1	Low	0.87 (0.80-0.94)**	0.93 (0.85-1.02)
	Moderate	0.76 (0.67-0.86)**	0.88 (0.76-0.97)*
	High	0.69 (0.63-0.76)**	0.75 (0.68-0.83)**
Model 2	Low	0.90 (0.82-0.98)*	0.97 (0.89-1.07)
	Moderate	0.82 (0.72-0.93)**	0.95 (0.83-1.09)
	High	0.77 (0.68-0.86)**	0.86 (0.76-0.97)*
Model 3	Low	0.98 (0.89-1.08)	1.01 (0.91-1.11)
	Moderate	0.85 (0.74-0.97)*	0.97 (0.85-1.11)
	High	0.84 (0.75-0.95)**	0.92 (0.82-1.04)

Model 1: Adjusted for age and sex. Model 2 Further adjusted for demographic factors, history of chronic disease and depressive symptoms. Model 3 additionally adjusted for health behaviours, sleep duration and BMI. ** p <0.001 * p <0.05

There are two separate measures of positive affect in the NHEFS study: the GWQ positive affect measure and CES-D positive affect subscale. To test whether we would find similar results with a different positive affect measure, we re-ran the analysis replacing the GWQ positive affect measure with the CES-D subscale. The interaction between perceived stress and positive affect was significant in the age- and sex-adjusted model ($p = 0.017$), but not in the model additionally adjusted for demographic factors ($p = 0.065$) or in the fully adjusted model ($p = 0.078$).

There is evidence that subdomains of depressive symptoms are differentially associated with health behaviours (Leventhal, Ramsey, Brown, LaChance, & Kahler, 2008). The CES-D can be divided into subdomains of negative affect, anhedonia and somatic symptoms (Carleton et al., 2013). To specifically test for the role of negative affect, we re-ran the analysis replacing CES-D with negative affect. As was the case for CES-D, negative affect was not a significant predictor of mortality risk in the fully adjusted model. The results for positive affect were very similar to those in our original analysis. In the fully adjusted model, HRs for positive affect in the moderate and high perceived stress tertiles were 0.01 unit lower than in the original analysis.

Proportional hazard assumptions were not met for age, history of cancer and BMI. To address this violation of the proportionality assumption, we re-ran the fully adjusted model using the step-approach method (Therneau, Crowson, & Atkinson, 2017). This approach allowed us to model the change in the effect of age, history of cancer and BMI over time. HRs for positive affect, perceived stress and the positive affect × perceived stress interaction were the same as in the original fully adjusted model.

Discussion

According to the stress buffering model, positive affect may protect against some health harming consequences of psychological stress (Pressman & Cohen, 2005). The link between higher positive affect and longevity may therefore be most pronounced among individuals who experience stress. In this large nationally-representative sample, we found a significant interaction between perceived stress and positive affect; the association between higher positive affect and longevity was strongest among participants who reported higher stress. This interaction remained significant following adjustment for depressive symptoms, demographic factors, history of chronic disease, and health behaviours. The strength of the association between positive affect and mortality risk was similar (and statistically significant) in the fully adjusted model for participants who reported moderate and high levels of stress. This finding suggests that even individuals with moderately elevated stress may benefit from positive affect.

There are various mechanisms that might account for the stress-buffering effect; positive affect may lessen HPA and ANS activity as well as health harming behavioural responses to stress (Pressman & Cohen, 2005). Although we were unable to test for physiological responses to perceived stress in our study, we did examine the effect of health behaviours. Adjusting for health behaviours attenuated the interaction effect between positive affect and perceived stress by 19% – suggesting that the stress buffering effect is partially explained by differential behavioural responses to stress. Specifically, individuals with high positive affect may be less likely to engage in health harming behaviours during periods of stress.

Pressman and Cohen (2005) further suggest that positive affect may reduce the experience of or exposure to psychological stress. This idea was supported by the strong negative correlation between positive affect and perceived stress in our study. However, as this association was cross-sectional, the direction of the relationship between perceived stress and positive affect is unclear.

It is also possible that the interaction between positive affect and stress is confounded by SES. Individuals with higher positive affect in our study also tended to have more wealth and more years of education. Prior research has identified SES as a key modifier of the association between stress and mortality risk; stress is most strongly associated with mortality risk in low SES groups (Lazzarino, Hamer, Stamatakis, & Steptoe, 2013). We found some evidence of a confounding effect in our study. Adjusting for wealth and education attenuated the interaction between perceived stress and positive affect by 11%.

The pattern of results in our study is similar to those of two cross-sectional studies. Specifically, Blevins et al. (2016) and Bränström (Bränström, 2013) found that the associations between higher positive affect and lower levels of inflammatory markers and better self-rated health, respectively, were stronger among participants who reported higher levels of stress. The current study builds on previous findings by demonstrating that a stress-buffering effect can be found in longitudinal data and for all-cause mortality risk. In addition, these data allowed us to adjust for potentially mediating or confounding variables, including physical activity, alcohol consumption, and diet, that were not included in previous cross-sectional studies.

Our results partially contrast with those reported by Moskowitz et al. (2008) who found that the association between higher positive affect and longevity did not differ as a function of perceived stress in participants without any chronic conditions and participants with diabetes. However, in a subsample of participants over the age of 65 with no chronic conditions, the positive association between positive affect and longevity was strongest among participants who reported higher stress. There are differences between our study and the study by Moskowitz et al. (2008) that might account for these divergent findings. First, the larger sample size (n = 8,542 vs 2,890) in our study may have increased our chance of detecting an interaction effect. Second, Moskowitz et al. (2008) used the positive affect subscale from the CES-D and we used the positive affect subscale from the GWQ. This may have made a difference because the CES-D subscale differs from the GWQ in that it contains questions regarding self-esteem and hope for the future (as well as happiness and enjoyment). In supplementary Cox regressions where we replaced the GWQ positive affect measure with the CES-D subscale, we found that the interaction between perceived stress and positive affect was significant in the age- and sex-adjusted model (p = 0.017) but not in the model additionally adjusted for demographic factors (p = 0.065) or the fully adjusted model (p = 0.078). It is possible that the type of positive affect measured in the GWQ (feeling in high spirits, happy, and full of energy) plays a greater role in buffering against the deleterious effects of stress.

There is evidence that the subdomain of energy/vitality may underlie associations between higher positive affect and longevity (Pressman & Cohen, 2005). To test whether this was the case in these data, we repeated the main analysis excluding the

vitality item from the GWQ positive affect measure. The interaction between perceived stress and positive affect in the fully adjusted model was not significant. This finding suggests that the vitality subdomain may have partially driven the negative association between positive affect and mortality risk. A previous longitudinal study documented an association between emotional vitality, defined as 'a positive state associated with feelings of enthusiasm, energy, and interest' (Kubzansky & Thurston, 2007, p. 1394), and lower risk of cardiovascular disease death (Kubzansky & Thurston, 2007). This study also used data from NHANES, emotional vitality was assessed with items from the General Wellbeing Schedule: 'Have you been waking up fresh and rested?' 'How much energy, pep, vitality have you felt?' 'How happy, satisfied, or pleased have you been with your personal life?' 'Has your daily life been full of things that were interesting to you?' 'Have you been in firm control of your behaviour, thoughts, emotions or feelings?' and 'Have you been feeling emotionally stable and sure of yourself?'. Kubzansky and Thurnstone (2007) suggested that, as well as dampening physiological responses to stress, high emotional vitality may confer cognitive (e.g., concentration or problem solving) and social advantages that help protect against mortality risk. However, it is also plausible that emotional vitality measures function as an index of physical vitality. Thus, physical rather than emotional health may account for the association between vitality and mortality risk.

According to the stress-buffering model, the experience of stress negatively impacts health. This prediction was only partially supported by our results. We found a positive association between stress and mortality risk in an age- and sex-adjusted

model. This association was not significant following adjustment for demographic differences, depressive symptoms, history of chronic disease and health behaviours – suggesting that these factors may account for the positive link between stress and mortality risk. Although the positive association between stress and risk of mortality from cardiovascular disease is relatively well established (Richardson et al., 2012), findings regarding the association between stress and all-cause mortality have been mixed. In a sample of 12,128 Danish participants, following adjustment for established risk factors, men with high stress had a higher risk of mortality; however, there was no association between stress and all-cause mortality risk among women (Nielsen, Kristensen, Schnohr, & Grønbæk, 2008). In a study of 4,132 Taiwanese older adults, the positive association between perceived stress and risk of all-cause mortality was not significant following adjustment for depressive symptoms, mobility limitations and medical conditions (Vasunilashorn, Glei, Weinstein, & Goldman, 2013). Surprisingly, in our study, the relationship between stress and mortality risk became inverse and significant following additional adjustment for positive affect. It is unclear why this was the case. However, as low positive affect was associated with a higher mortality risk and participants with higher perceived stress reported lower positive affect, it is possible that positive affect partially confounded the positive association between perceived stress and mortality risk. Although reports of stress have generally been linked with poorer health outcomes, there is evidence that the experience of (short-term) moderate stress can be beneficial (J. Liu & Vickers, 2015). Liu and Vickers (J. Liu & Vickers, 2015) suggest that the experience of moderate stress may help individuals become more resilient. High

resilience has been linked to favourable health outcomes (Chen & Miller, 2012; Tugade, Fredrickson, & Feldman Barrett, 2004).

The temporal relationship between positive affect and perceived stress was unclear in our study as participants were asked to report the degree to which they experienced positive affect and stress within the past month. Positive affect could have preceded, followed or co-occurred with the experience of stress. Further work is needed to investigate the relationship between positive affect and physical health at each of these time points. Notably, although perceived stress and positive affect were assessed at one time point in our study, the interaction between these variables in predicting mortality risk was apparent over the 10-year follow-up period. This suggests that our findings reflect relatively stable (i.e., trait) differences in perceived stress and positive affect. Previous work shows that positive affect is closely related to personality (specifically, extraversion) (R. J. Larsen & Ketelaar, 1991) and can remain stable even over long periods of time (20 years) (Charles et al., 2001). To explore this further, we examined the stability of positive affect and perceived stress measures between NHANES 1 and NHEFS (1982) (perceived stress and positive affect were not measured in subsequent waves of the NHEFS). Surprisingly, the measures were only moderately stable; the test-retest reliability was 0.43 for positive affect and 0.42 for perceived stress.

The stability of positive affect and stress may vary as a function of age. Although positive affect and perceived stress can remain stable through much of adult life, previous studies have documented a decline in positive affect and an increase in perceived stress among those aged 65 and over (Charles et al., 2001; Osmanovic-

Thunström, Mossello, Åkerstedt, Fratiglioni, & Wang, 2015). Future studies could test whether the interaction between positive affect and stress in predicting mortality risk is consistent across different age groups.

The stress measure in our study was subjective rather than objective. Holme and Rahe's (1967) Social Readjustment Rating Scale – which requires participants to indicate the number of pre-defined stressful events they have experienced – could provide a more objective alternative. However, previous work indicates that, compared with stressful life event measures, subjective measures of stress – that are sensitive to individual differences in appraisal – are more strongly related to mental and physical health (Sin, Graham-Engeland, Ong, & Almeida, 2015). It should also be noted that the subjective stress measure in our study was strongly positively correlated with depressive symptoms and strongly negatively correlated with positive affect.

Our study had several strengths, including the use of a large nationally representative sample, the fact that mortality data were obtained from death certificates rather than by proxy reports, and the availability of many measures that enabled us to control for potential confounds. One limitation of our study was that a substantial proportion of participants were excluded due to missing data. This may have introduced a source of bias as excluded participants differed from included participants on several covariates (see table 6.1). Analysis with imputed missing covariate data yielded largely similar effect sizes to those obtained from analysis with complete data; however, the interaction between positive affect and stress in predicting mortality risk was not significant in the fully adjusted model. In addition, our perceived stress

measure was not sensitive to the cause or duration of stress. Both of these factors affect the strength of association between stress and physical health and warrant consideration in future studies (Schneiderman et al., 2005).

Conclusion

Our findings in this chapter indicate that the positive association between positive affect and longevity may not be universal, but depend on perceived stress, and possibly other psychosocial processes. Research concerning links between positive affect and mortality risk should test for the presence of stress buffering mechanisms. On a practical note, authors have proposed that interventions designed to increase positive affect may promote health among older adults (Boehm et al., 2011; Howell et al., 2007). Our results suggest that such interventions may be most effective among groups who report high levels of stress.

Chapter 7: General Discussion

Over the past decade, researchers have built up a substantial body of evidence demonstrating an association between higher wellbeing and favourable health outcomes including lower disease risk and greater longevity. The purpose of this thesis was to clarify the nature of this association. To this end, we tested whether wellbeing is associated with the risk of specific chronic physical diseases and examined potential mediators and moderators of the association between wellbeing and disease or mortality risk. In this final chapter, we discuss our findings in light of these research objectives, highlight limitations regarding our samples and methodological approach, and finally, consider potential directions for future research.

Wellbeing and chronic disease risk

In chapters 2 and 3, we used data from the English Longitudinal Study of Ageing (ELSA) and the Survey of Health, Ageing and Retirement in Europe (SHARE) to examine the association between wellbeing and the risk of arthritis, stroke, heart attack, cancer, diabetes and chronic lung disease. Previous studies have documented an association between wellbeing and cardiovascular disease (Feller et al., 2013; Sin, 2016), cancer (Feller et al., 2013; Wakai et al., 2007) and type 2 diabetes (Feller et al., 2013; Shirom et al., 2012). The findings described in chapters 2 and 3 build on previous research in two ways; firstly, by demonstrating that wellbeing is additionally associated with risk of arthritis or chronic lung disease, and secondly, by indicating that the association between wellbeing and disease risk may be disease dependent. We found that wellbeing was most strongly associated with the risk of

arthritis, diabetes and chronic lung disease; we observed weaker associations between wellbeing and risk of stroke or heart attack, and no association between wellbeing and risk of cancer. This finding could contribute to the development of explanatory models of the link between wellbeing and mortality risk. Previous studies have documented a link between higher wellbeing and a lower risk of all-cause mortality (Martín-María et al., 2017). One possible explanation of this association is that wellbeing is related to multiple forms of ill health that, in turn, increase mortality risk. This explanatory model is termed 'general susceptibility' and is commonly used in social epidemiology (Davey Smith, Gunnell, & Ben-Shlomo, 2001). Our finding – that wellbeing is associated with the risk of some chronic diseases and not others – could indicate that the link between wellbeing and mortality risk is driven by disease specific associations. However, our results should be interpreted with caution. Our findings differ from those of a previous study into life satisfaction and risk of incident diabetes, cancer, stroke or heart attack (Feller et al., 2013). This previous study found that life satisfaction was most strongly associated with risk of cancer and stroke. Thus, further work is needed to confirm which chronic diseases are most strongly linked to wellbeing, and, to explore potential mechanisms that might account for these disease specific associations.

Mediating and confounding variables

In chapters 2 and 3, we also examined the extent to which potentially mediating and confounding variables account for associations between wellbeing and disease risk. Although results varied according to the disease outcome, we generally found that adjusting for depressive symptoms, SES and health behaviours attenuated the

association between wellbeing and disease risk. Depressive symptoms and SES may be confounds of this risk association; however, it is possible that health behaviours act as mediators. That is, the experience of high wellbeing may motivate people to engage in health protective behaviours, such as eating well or exercising regularly (Pressman & Cohen, 2005). Future mediation studies could test for this effect.

In chapter 4, we examined the effect of another potential mediator. Using data from ELSA, we tested whether inflammatory mechanisms mediate the association between wellbeing and arthritis risk. In support of the idea that associations between wellbeing and health are partly mediated by psychobiological processes, we found evidence of a small mediation effect. The inflammatory marker CRP accounted for a small proportion (12%) of the association between wellbeing and arthritis risk. Wellbeing may impact multiple inflammatory mechanisms related to arthritis risk; however, data on only two inflammatory biomarkers (CRP and fibrinogen) were available to us. Thus, the magnitude of the effect in our study may be an underestimate of the extent to which inflammatory processes mediate the association between wellbeing and arthritis risk more generally. Studies that assess a wide range of biomarkers in addition to wellbeing and disease incidence, would help address this issue.

We treated health behaviours and inflammatory markers as potential mediators of the association between wellbeing and disease risk; however, the direction of association between these variables is not clear. Health behaviours may have had a confounding rather than mediating effect. That is, people who engage in healthy behaviours may enjoy higher wellbeing and better health as a consequence. In support of this idea,

there is evidence, from intervention studies, that attending organised physical activities can increase wellbeing among older adults (Netz, Wu, Becker, & Tenenbaum, 2005). We posited that wellbeing might influence disease risk by impacting inflammatory processes. However, it is also possible that early, undiagnosed, disease processes that affect levels of inflammation, negatively impact wellbeing via the influence of inflammation on negative psychosocial factors. Previous studies have documented a positive association between levels of inflammation and risk of fatigue, hostility and depression (Raison et al., 2006; Suarez et al., 2004). Finally, it is possible that shared genes influence both wellbeing and physiological processes, or health behaviours.

Moderators of the association between wellbeing and mortality risk

In chapter 5, we used data from SHARE to examine the association between wellbeing and mortality risk in 11 European countries that ranged widely in the degree to which they were individualistic versus collectivistic. We found a stronger association between wellbeing and self-rated health or risk of mortality from cardiovascular disease among more individualistic countries. This finding suggests that the strength of association between wellbeing and health may be culturally dependent. Our study also raised a methodological issue relevant to wellbeing and health research; namely, the potential effect of cultural bias in how wellbeing is measured. Wellbeing measures that rely on concepts more highly valued in more individualistic cultures, such as autonomy or sense of control, may not capture wellbeing in more collectivist cultures which value social interdependence and group loyalty (Hofstede et al., 1997).

Previous studies documented a stronger association between positive affect and self-rated health or biomarkers of health under conditions of higher stress (Blevins et al., 2016; Bränström, 2013). In chapter 6, we used data from the National Health and Nutrition Examination Study I (NHANES I) Epidemiologic Follow-Up Study (NHEFS) to test whether stress moderates the association between positive affect and mortality risk. We found a significant interaction between positive affect and perceived stress such that the association between positive affect and mortality risk was stronger in people reporting higher stress. This result provides additional support for the model that posits that wellbeing is associated with good health because it protects against the health-harming effects of perceived stress (Pressman & Cohen, 2005).

Sub-domains of wellbeing

Finally, as outlined in the introduction, it is not yet clear whether different domains of wellbeing (i.e. hedonic and eudemonic) are differentially associated with health outcomes. Although there is a high correlation between hedonic and eudemonic wellbeing, these are empirically separable constructs (Keyes, 2002) with some distinct predictors (Baumeister et al., 2013). In chapter 2, we examined the association between CASP-19 subdomains (control, autonomy, self-realisation and pleasure) and disease risk. Following adjustments for established risk factors, we found that eudemonic (control, autonomy, self-realisation) but not hedonic (pleasure) measures of wellbeing were associated with the risk of some chronic diseases. However, our results should be interpreted cautiously as most of these associations did not survive correction for multiple comparisons. The possibility that physical

health is more closely related to eudemonic, is supported by a previous study into eudemonic and hedonic wellbeing and mortality risk. In a sample of 6,163 American adults, Hill and Turiano (2014) found that, when both wellbeing measures were included in the same model, eudemonic but not hedonic wellbeing was significantly related to a lower risk of mortality. We did not distinguish between hedonic and eudemonic wellbeing in chapters 3 to 5; however, as the measure of wellbeing (the CASP-12 in chapters 3 and 5, and the CASP-19 in chapter 4) included a eudemonic component, it is possible that our findings in these chapters were also driven by eudemonic rather than hedonic wellbeing. In chapter 6, we observed a significant association between higher hedonic wellbeing and lower mortality risk – particularly among participants who reported higher levels of stress. Results from this chapter suggest that hedonic wellbeing is also related to mortality risk; however, we could not test for the effect of eudemonic wellbeing in this analysis. Identifying which domains of wellbeing are prospectively related to health will be an important next step. This knowledge could provide further insight regarding the mechanisms linking wellbeing and health, and potentially, inform the development of interventions which target aspects of wellbeing most closely related to health.

Limitations

Sample limitations

The samples described in this thesis shared several limitations. We excluded a significant proportion of participants from our study samples due to missing data on wellbeing, the covariates or the outcome variable (either vital status or disease incidence). The proportion of participants excluded due to missing wellbeing or

covariate data ranged from 14 to 55%. Participants who were excluded tended to be older, reported more depressive symptoms, had a lower SES and a higher prevalence of some chronic conditions. Thus, although we used data from samples designed to be representative of the older population in England, Europe or the U.S., excluding participants from our analytical samples may have introduced bias. We ran analysis to test for this effect. In chapter 2, this analysis consisted of sensitivity tests. For each disease outcome, the age- and sex-adjusted model was re-run including participants with missing covariate data. The results were very similar to those obtained in the sample with complete data. We also tested for bias due to the exclusion of participants with missing wellbeing data. In an age- and sex-adjusted model, missing wellbeing data did not predict incident arthritis, stroke, diabetes or heart attack; however, participants with missing wellbeing data were significantly more likely to develop chronic lung disease and were less likely to be diagnosed with cancer. In other chapters, we used multiple imputation to impute data on missing covariates and wellbeing. We found that results from analysis with complete data were similar to those from analysis that included participants with imputed data.

Overall, the results from this additional analysis suggested that excluding participants due to missing covariate or wellbeing data did not bias our results. However, we could not rule out the effect of bias due to missing data on the outcome variable (disease incidence or vital status).

Methodological limitations

All the studies described in this thesis were observational. This approach limited our ability to test for a causal association between wellbeing and disease or mortality risk as unmeasured factors (including work environment, early life experiences and genetic influences) may have confounded this association. A further issue relevant to our methodological approach, is that of statistical over-adjustment. In all our studies, we adjusted for the prevalence of health conditions that were likely to co-occur with or precede the outcome (mortality or disease incidence), and impact wellbeing. This allowed us to control for the potentially confounding effect of comorbid conditions. However, as participants reported health conditions and wellbeing at the same time point, the direction of association between these variables was unclear. It is also possible that earlier levels of wellbeing impacted the risk of comorbid conditions, and therefore, controlling for these conditions resulted in an under-estimation of the strength of association between wellbeing and disease or mortality risk.

Future Directions

Crucial questions regarding the association between wellbeing and later health remain. Specifically, further research is needed to identify the mechanisms that underlie this association, and, ultimately to test whether wellbeing interventions will lead to better health. Addressing these problems will require observational and experimental approaches. Here, we outline suggestions for future studies and highlight some potential challenges that lie ahead.

An important limitation of studies into wellbeing and health is that most, including those described in this thesis, utilise secondary data. Consequently, researchers have

used measures of wellbeing that are available, rather than optimal for their research question. With the development of new studies, there is an opportunity to introduce measures of wellbeing more suitable to research into wellbeing and health.

Choosing an appropriate measure of wellbeing requires several considerations. Firstly, a primary concern of any measure of wellbeing is that of construct validity. Wellbeing can be defined as the experience of positive emotions, and, living fully to one's potential and values. While assessing hedonic wellbeing i.e. the experience of positive emotions, may be relatively straightforward, measurement of eudemonic wellbeing i.e., living fully to one's potential and values, can be more complicated. This is because 'feeling good' is arguably a universal experience, whereas what constitutes achieving one's potential is likely to depend on many factors including one's culture and life experiences. We touched on this issue in chapter 5, where we argued that questions regarding control and autonomy may not capture eudemonic wellbeing among people from collectivist cultures.

The challenge of assessing eudemonic wellbeing has been approached in two ways. Some researchers have addressed this issue by developing wellbeing measures which are appropriate to the specific context in which they are applied. Assessing wellbeing in this way requires researchers to make assumptions regarding the indicators of eudemonic wellbeing, and potentially, the context in which they should be assessed. The CASP-19 (Hyde et al., 2003), which is designed to assess hedonic and eudemonic wellbeing in older populations, is an example of this approach. As outlined in the introduction, the CASP-19 is based on a needs satisfaction model of wellbeing, whereby the experience of wellbeing is dependent on the satisfaction of

four needs: control, autonomy, self-realisation and pleasure. Some CASP items assess the extent to which these needs are met in specific contexts e.g., freedom from family responsibilities or financial concerns (see table 1.1). A potential limitation of this approach is that it is too prescriptive, and therefore fails to capture wellbeing among respondents who achieve eudemonic wellbeing through means and contexts other than those outlined by the CASP-19. An alternative approach, advocated by Deiner, Sapyta, and Suh (1998), is to assess life-satisfaction. The authors argue that this approach provides a valid index of eudemonic and hedonic wellbeing, while allowing the respondent, rather than the researcher, to identify the determinants of positive functioning. However, a limitation of this approach is that there is no clear distinction between the sub-domains of hedonic and eudemonic wellbeing.

Wellbeing measures should also allow researchers to explore outstanding questions regarding the association between wellbeing and health. To this end, measures which distinguish between the different domains of wellbeing (i.e., hedonic and eudemonic) would be beneficial. Including hedonic and eudemonic measures in the same model would allow researchers to test which wellbeing component is most strongly related to health, and, examine how these subdomains might interact in predicting health. A final issue worth considering, is that of construct overlap, specifically in relation to physical health. For instance, both measures of wellbeing used in this thesis (the CASP-19 and positive affect sub-scale) included items which could reflect levels of physical health: ‘How much energy, pep, vitality have you felt during the past month?’ and ‘My health stops me from doing the things I want to do’. These items are problematic in the context of research into the association between wellbeing and

health, as risk associations could be influenced by physical rather than psychological wellbeing. We were able to control for this effect by excluding responses to health-related items from our analyses. However, future studies may benefit from using wellbeing measures which are distinct from measures relating to physical health.

In sum, a wellbeing measure should capture wellbeing in the target population, be distinct from indicators of physical health, and, allow researchers to differentiate between hedonic and eudemonic aspects of wellbeing. Achieving this aim requires a compromise between the measure's generalisability (the extent to which the measure captures wellbeing across individuals) and specificity (the extent to which the measure differentiates between different aspects of wellbeing, or is separable from other domains or functioning). The Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) is an example of this approach. This 14 item scale assesses hedonic and eudemonic aspects of wellbeing (Clarke et al., 2011). As in the CASP-19, eudemonic wellbeing is defined in terms of personal relatedness, meaning and purpose. However, in contrast with this former measure, WEMWBS items do not reference specific contexts such as financial concerns or family life, and as such, may provide a more sensitive measure of wellbeing. At the between country or culture level, the issue of construct validity may be best addressed by the use of eudemonic wellbeing measures which are appropriate to the specific cultural context in which they are applied. Such measures are now becoming available. For example, the Interdependent Happiness Scale (IHS) is designed to assess wellbeing in collectivist cultures (Datu et al., 2016).

A further important consideration regarding observational studies of wellbeing and health, relates to the timing of longitudinal cohort studies. The association between wellbeing and health may only become apparent in older age as many chronic diseases manifest themselves in later life. However, it is likely that this association results from processes acting across the life course. Studies that incorporate a life course approach may therefore provide further insight regarding the causal pathways between wellbeing and health. For instance, such studies could test whether early childhood experiences confound subsequent associations between wellbeing and later health. Research indicates that experiences in childhood (including childhood illness and family psychosocial environment) predict wellbeing and health in adulthood (Conti & Heckman, 2013; Haas, 2007; Stafford et al., 2015). Researchers could also test whether the experience of wellbeing in childhood or adolescence impacts disease processes in adulthood. Previous studies indicate that other positive psychosocial factors in childhood, including social adjustment and perceived social support, are associated with cardiometabolic health in adulthood (Pulkki-Råback et al., 2015; Slopen, Chen, Priest, Albert, & Williams, 2016). On a related point, future studies could examine whether there is a stage of development, when wellbeing is most strongly related to subsequent health. Previous studies have identified such critical periods, for example, Davey Smith, Gunnell and Ben-Shlomo (2001) found that risk of stomach cancer and stroke was strongly influenced by early life SES.

Life course studies into wellbeing and health should be complemented by intervention studies. Specifically, further work is needed to confirm that wellbeing is causally related to health and to test whether wellbeing interventions will lead to

better health. Research in this area is at an early stage. However, there is evidence that interventions can improve wellbeing in older adults. Effective approaches include promoting physical activity (Netz et al., 2005), participation in learning (Jenkins & Mostafa, 2013), the expression of optimism or gratitude (Lyubomirsky, Dickerhoof, Boehm, & Sheldon, 2011) and mindfulness (Keng et al., 2011). Although longer term follow up studies are needed, there is evidence that improvements in wellbeing associated with positive psychology interventions, can be sustained for at least 6 months (Proyer, Gander, Wellenzohn, & Ruch, 2014). In addition, there is evidence that eliciting positive emotion in the lab can impact immune, endocrine and cardiovascular functioning (Diener & Chan, 2011). However, large randomised control trials are needed to establish whether wellbeing interventions can have long term health consequences (Sin, 2016).

Assuming wellbeing interventions can impact health, there are problems that should be addressed. Firstly, interventions that have comparable effects on wellbeing may have differential consequences in terms of health (Hernán & Taubman, 2008). This is because some wellbeing interventions, for example, promoting physical activity, are likely to have effects on health that are not mediated by wellbeing. Researchers should aim to identify methods that provide the greatest health benefits. Secondly, researchers should develop interventions at the societal and individual level. Ultimately, wellbeing is closely linked to social circumstances (Trudel-Fitzgerald, Qureshi, Appleton, & Kubzansky, 2017). Thus, interventions that address the determinants of wellbeing at the societal level may be more effective in terms of promoting health and addressing health inequalities. Finally, in combination with

findings from longitudinal observational studies, randomised controlled studies should be developed to identify the life stage at which wellbeing interventions may be most beneficial.

Conclusion

Current findings regarding the association between wellbeing and later health indicate that these factors are linked. Wellbeing is related to a cluster of factors including health behaviours, social resources and physiological processes that are also implicated in the development of disease. As such, the construct of wellbeing may prove a powerful tool for understanding health disparities, and potentially, for developing health interventions. The studies described in this thesis demonstrate that the link between wellbeing and health may not be universal. Rather, wellbeing may be related to specific health outcomes and this association may depend on other psychosocial processes. These findings contribute to the field of wellbeing research by illustrating that the construct of wellbeing cannot be defined or studied in isolation of the wider biological or psychosocial context. Further work is needed to explore potential pathways from wellbeing to health and to test the efficacy of wellbeing interventions. We hope our findings will help guide the direction of these future investigations.

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