Lifetime affective symptoms and mortality in the MRC National Survey of Health and Development

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Declaration of Authorship

I, Gemma Archer, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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ABSTRACT

This thesis investigated associations between lifetime affective symptoms and mortality in the MRC National Survey of Health and Development (NSHD; the British 1946 birth cohort). Affective symptoms were initially rated by teachers when study members were aged 13 and 15; then by semi-structured clinical interview at age 36 using the Present State Examination (PSE); the interview-based Psychiatric Frequency Questionnaire at age 43; and the self-report 28-item General Health Questionnaire at age 53. Mortality data including cause of death was obtained from the NHS Central Register. Follow-up time was from ages of exposure to end of October 2014 (age 68). A wide range of covariates were tested, including sex; early life factors; adult health indicators and health behaviours; psychotropic medication; stressful life events, and social factors. Cox regression showed that after adjustment for sex, severe affective symptoms were associated with an increased risk of mortality compared to those with no or mild symptoms across most ages. There was evidence of an accumulation effect where the risk of mortality increased as affective caseness increased. Adolescent-only, intermittent and chronic caseness were associated with increased risk of mortality compared to those who were never a case. There was a slightly stronger association between affective caseness and cardiovascular mortality compared to cancer mortality; however the strongest associations appeared to be with respect to deaths from 'other' causes. After full adjustment, those who were a case at a single point in time and those with adolescent-only caseness had a 46% and 73% increased risk of mortality respectively, compared to those who were never a case. All other associations were largely explained by the covariates, with most relationships attenuated predominantly by self-reported health conditions, physical activity, lung function, smoking, and psychotropic medication use. These results demonstrate the inherent interplay between affective symptoms and physical health, and highlight the importance of early intervention in order to reduce health inequalities.

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INTRODUCTION

Associations between affective symptoms and mortality have been shown among psychiatric, medical, and community based samples, and across many causes of death; however the large majority of studies have relied on a single measure of affective symptoms in mid-life or older adulthood. Studies incorporating repeated measures of affective symptoms have been conducted among older persons, and over a relatively short follow-up, and almost no studies have taken into account the timing of affective symptoms – which could potentially govern pathways to mortality. As such, relatively little is known about the relationship between mortality and affective symptoms in adolescence or early-adulthood or if the timing of affective symptoms is important over the life course. Furthermore, most studies have controlled for only a handful of covariates, which means that there is limited understanding of explanatory pathways. This thesis will use the MRC National Survey of Health and Development (NSHD), which is unique in having measures of affective symptoms spanning from adolescence to late-adulthood, in addition to data on a wide range of potential explanatory factors. This thesis will therefore enrich the current literature by firstly examining which factors characterise the relationship between affective symptoms and mortality over the life course; for instance the severity, chronicity and timing of affective symptoms; and secondly by building a greater understanding of potential social, behavioural and physiological explanatory pathways.

The thesis is structured as follows: Chapter 1 begins by introducing affective symptoms, including their definition, prevalence and measurement, followed by a review of the literature on affective symptoms and mortality. Chapter 2 outlines the objectives, aims, and hypotheses. Chapter 3 introduces the dataset, discusses general methodological issues, and describes the variables used in analyses and how they were derived. Chapter 4 is the first of four empirical chapters and investigates if the relationship between affective symptoms and mortality varies across age or by symptom severity. Imputed data is then used for all subsequent analyses: Chapter 5 tests whether there is an accumulation effect over the life course with regard to affective caseness and mortality, in addition to examining potential behavioural, social, and physiological pathways. Chapter 6 investigates the role of affective case history (the timing of an affective case) with regards to mortality, and again potential explanatory pathways are explored. The final empirical chapter, Chapter 7, tests whether the associations between mortality and affective case accumulation and affective case history are moderated by cause of death. This is followed

by an overall discussion chapter, in which the results are summarised and recommendations made for future research and policy.

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List of abbreviations

BMI Body mass index

bpm Beats per minute

CI Confidence Interval

CMD Common Mental Disorder

CRP C-reactive protein

DSM **Diagnostic and Statistical Manual of Mental Disorders**

FEV_1 Forced Expiratory volume in one second

GHQ General Health Questionnaire

HR Hazard ratio

kg/m^2 Kilograms per meter squared

mmHg Millimetres of mercury

NSHD National Survey of Health and Development (1946 British birth cohort study)

OR Odds ratio

PSE Present State Examination

PSF Psychiatric Symptom Frequency scale

RR Risk ratio

SD Standard deviation

SHR Sub-distribution hazard ratio

SSRI Selective serotonin reuptake inhibitor

TCA Tricyclic antidepressant

χ^2 Chi-squared

1. LITERATURE REVIEW

1.1 Chapter overview

This chapter begins by introducing affective symptoms with respect to their definition, prevalence, longitudinal typologies, measurement, and issues relating to diagnosis of disorders. The literature is reviewed firstly with respect to factors that characterise the nature of the relationship between affective symptoms and mortality, such as the severity of affective symptoms, history of affective symptoms, the study population, and cause of death. Secondly, potential explanatory pathways are discussed with respect to social, behavioural, and physiological mechanisms, and a conceptual model is proposed. Finally, the rationale for the thesis is presented.

1.2 Introduction: Affective symptoms

1.2.1 Definition

Affective symptoms refer to symptoms of depression and anxiety, which are frequently experienced in the general population. Severe affective symptoms may interfere with daily functioning and indicate the presence Common Mental Disorder (CMD), which comprises different types of anxiety and depressive disorders (National Institute for Health and Clinical Excellence, 2011).

This thesis will focus on mood disturbance only, and will not attempt to assess the primary role of symptoms relating to other forms of mental illness, such as psychotic disorders, personality disorders, or substance misuse.

The large majority of existing literature on mental health and mortality concerns depression, which will be the focus of this chapter; however it should be noted that anxiety and depressive symptoms often co-occur (consistent with the concept of CMD, and discussed in detail in section 1.2.4)

1.2.2 Prevalence and public health

Psychiatric disorder is an increasingly large public health issue. Depression currently ranks as the leading cause of disability in middle and high income countries (World Health Organization, 2015), and by 2020 is estimated to become the second largest global burden of disease (Murray and Lopez, 1997). Disease burden is assessed using the disability-

adjusted life-year (DALY) which is a single measure combining years of life lost from premature death and the years of life lost due to disability and poor health. In the UK, mental disorder is responsible for almost half of all ill health among those aged under 65, and accounts for 23% of the total burden of disease (Layard, 2012).

The National Comorbidity Study (Kessler et al., 2005) investigated the lifetime prevalence of psychiatric disorder in the United States. Anxiety disorders were most common (28.8%), followed by mood disorders (20.8%), whilst the lifetime prevalence of any psychiatric disorder was 46.4%.

In the UK, the Adult Psychiatric Morbidity Survey (McManus et al., 2009) found that the point prevalence of adult Common Mental Disorder (CMD) was 16.2%. More than half of those with CMD had mixed anxiety and depressive disorder (9.0%). The next most prevalent was generalised anxiety disorder (GAD, 4.4%), followed by depression (2.3%). Women were more likely than men to reach criteria for CMD (19.7% and 12.5%, respectively), which is consistent with other studies across many different countries and cultures (Culbertson, 1997; Piccinelli and Wilkinson, 2000). CMD appeared to be less common at older ages; the prevalence of CMD was 18.2% for ages 16-34 years; 17.3%, for ages 35-44 years; 19.9% for ages 45-54 years; 14.1% for ages 55-64 years; and 10.6% among ages 65-74 years (McManus et al., 2009).

1.2.3 Longitudinal typology

The continuity of psychiatric disorders from childhood to adulthood has been demonstrated by numerous studies that have followed-up individuals who attended psychiatric services as children (Mellsop, 1973; O'Neal and Robins, 1958; Pritchard and Graham, 1966). Substantial continuity has been found between depression experienced in adolescence and depression in adulthood (Harrington et al., 1990; Zeitlin, 1986), and similar findings have been reported with respect to population-based samples (Colman et al., 2007b; Rutter, 1989; Rutter et al., 1976). In the National Survey of Health and Development (NSHD; see section 3.2 for study description), approximately seventy percent of those who experienced internalising problems in adolescence had mental disorder in adulthood, compared to only twenty-five percent who had no adolescent mental health problems (Colman et al., 2007b).

Depression has also been shown to be a highly recurrent disorder throughout adulthood (Birmaher et al., 1996; Paykel, 1994). Among the general population, approximately half of

those who recover from an initial episode of depression will have one or more further episodes in their lifetime (Eaton et al., 2008; Hardeveld et al., 2013), with higher rates of relapse observed among clinical populations (Hardeveld et al., 2010; Kennedy et al., 2003). The strongest predictors of relapse have been found to be clinical factors such as a greater number of previous episodes, the severity of prior symptoms, and an earlier age of onset (Hardeveld et al., 2013, 2010).

Only one study, using the NSHD data, has prospectively examined longitudinal trajectories using multiple measures of affective symptoms from adolescence to late-adulthood. Colman et al., (2007a) performed longitudinal latent class analysis on measures of anxiety and depressive symptoms at ages 13, 15, 36, 43, and 53 years. Six different profiles were identified: absence of symptoms (44.8% of sample); adolescent symptoms with good adult outcome (5.8%); repeated moderate symptoms (33.6%); repeated severe symptoms (1.7%), adult-onset moderate symptoms (11.3%); and adult-onset severe symptoms (2.9%). These results show that of those who experienced moderate or severe affective symptoms, approximately 65% had recurrent symptoms over their lifetime.

1.2.4 Classification of anxiety and depressive disorders

Classification of mental disorder is dominated by the Diagnostic and Statistical Manual of Mental Disorders in the USA, now in its fifth revision (American Psychiatric Association, 2013), and in Europe by the International Classification of Diseases, currently in its tenth revision, which also covers non-psychiatric disorders (World Health Organization, 1992). Psychiatric disorders are normally identified using a set of criteria which specify what particular symptoms must be present, in addition to a list of other symptoms and conditions which must be ruled out in order to make a diagnosis.

Depression (major depressive disorder) is usually defined by the presence of depressed mood or loss of interest in pleasurable activities for at least two weeks, which may be accompanied by other symptoms such as weight loss or gain, fatigue, feelings of worthlessness or guilt, insomnia, suicidal thoughts, inability to concentrate or make decisions, and psychomotor agitation (American Psychiatric Association, 2013). Symptoms of anxiety typically include excessive worry, fear, restlessness, irritability, feeling on edge, muscle tension, and difficulty falling asleep. Anxiety disorders are diagnosed when symptoms last six months or longer, and the fear or anxiety is out of proportion to the situation and interferes with daily activities (American Psychiatric Association, 2013).

Categorising mental disorders has several advantages: it can help physicians to establish appropriate interventions for their patients, researchers to study the aetiology and course of illness, and patients to better understand their symptoms (Farmer et al., 2002); however there is also evidence to suggest that the categorical approach is flawed. For instance, there is little support for the concept of mutually exclusivity – studies have consistently shown high levels of co-morbidity between psychiatric disorders (2005; Kessler et al., 1994; Robins et al., 1991; Sartorius et al., 1996; Vollebergh et al., 2001) with particularly strong associations observed between anxiety and depression. In the US National Comorbidity Study, over half of those with major depression in the previous year also reported an anxiety disorder during this period (Kessler et al., 1996), whilst other studies have demonstrated a higher prevalence of comorbid anxiety and depression compared to each disorder alone (Merikangas et al., 1996; Singleton et al., 2003). Notably, anxiety has been found to be primary to depression in the majority of comorbid cases (Kessler et al., 2005; Wittchen et al., 2003, 2000), suggesting that anxiety symptoms may precede depression. Self-report questionnaires and clinical interviews have also shown strong correlations between measures of anxiety and depression (Clark and Watson, 1991; Goldberg et al., 1987) and several studies using factor and latent structure analysis have suggested that generalised anxiety disorder, major depression, and dysthymia are best represented by a single underlying construct, namely 'anxious misery disorders' (Krueger et al., 1998; Vollebergh et al., 2001).

Further evidence of a strong relationship between anxiety and depression comes from studies which have shown that the antecedents of each disorder are not dissimilar. In the NSHD, Richards and Goldberg (2010) found little evidence that early adverse exposures, such as childhood illness, parental separation, and parental health, differentiated study members with respect anxiety or depressive symptoms experienced in midlife, with similar findings reported in US studies with respect to sociodemographic factors and stressful life events (Eaton and Ritter, 1988). Notably, Richards and Goldberg's study formed part of a larger consultation by the American Psychiatric Institute for Research and Education (APIRE) who brought together a panel of international experts to help clarify the relationship between generalised anxiety disorder and depression. They concluded that "however close or distant the disorders are, the causes of each are almost the same, and the symptom dimensions themselves are closely related" (Goldberg, 2010, p. 360). These findings are also consistent with twin studies which have shown that anxiety and depression share common genetic factors, whereby genes implicated in depression and

anxiety have been found to be completely shared between the two disorders (Kendler et al., 1992, 1987; Leonardo and Hen, 2006).

Strong overlap between anxiety and depression led to use of the term 'Common Mental Disorder' (CMD) (Goldberg and Huxley, 1992). Many studies have shown no advantage in distinguishing between symptoms of anxiety and depression (Shorter and Tyrer, 2003; Tyrer, 2001, 1990); therefore this thesis will focus largely on affective symptoms, consistent with the concept of CMD.

1.2.5 Measurement in epidemiological studies

Anxiety and depressive disorders are usually diagnosed in epidemiological studies using a structured clinical interview, or identified through hospital admission data; although these measures often fail to capture those with moderate, or sub-clinical symptoms (Farmer et al., 2002; McDowell, 2006). The majority of clinical and population based studies rely on self-report screening questionnaires to establish the presence of affective symptoms. Scores can range from mild through to severe, and often validated cut-points are used to determine the likelihood psychiatric disorder. These scales have several limitations, however, which can lead to measurement error. For example, current symptoms or symptoms over the last week/month are usually assessed, which means that questionnaires are not able to distinguish between transitory psychological states and lifetime disorders. Many scales also contain somatic items, whilst others contain none; this can make comparability between questionnaires difficult, especially if somatic items tap symptoms driven by poor physical health (McDowell, 2006).

1.3 Affective symptoms and mortality

1.3.1 Psychiatric disorders, depressive symptoms, and mortality

There is established evidence of major health inequalities between people with psychiatric disorders compared to general population averages. Among Nordic countries, Wahlbeck et al., (2011) calculated that men admitted to psychiatric hospital could expect to live 20 years less, and women 15 years less than the general population average. This mortality gap has remained largely unchanged over time and was observed across many causes of death. Similar results have been demonstrated in the UK; Chang et al., (2011) found that those in contact with mental health services had considerably lower life expectancies compared

with the national population. 'Depressive episode and recurrent depression' was associated with a 10.6 year lower life expectancy in men, and a 7.2 year lower life expectancy in women, although the highest reductions were seen among those with schizophrenia and schizoaffective disorders.

There have been numerous studies exploring the relationship between depression and mortality among non-psychiatric populations, although the findings are less consistent. Wulsin et al. (1999) conducted a large systematic review and meta-analysis of 51 studies including community, medical, and also psychiatric based samples; the authors identified 18 high-quality medical and community-based studies, of which only 44% reported a positive association between depression and mortality. Likewise, a systematic review of 12 studies among older medical inpatients demonstrated a similar pattern (Cole, 2007). Mixed results have been attributed to differences in study design, study population, covariates, cause of death, measure of depression, and length of follow-up (Cole, 2007; Wulsin et al., 1999).

Wulsin et al. (1999) were unable to identify any observable trends across studies, other than that associations appeared stronger among psychiatric samples (average RR=2.7), compared to community settings (average RR=1.2). Whilst this could be attributed to symptom severity, it is notable that psychiatric studies were adjusted for age and sex only, whilst community-based studies were adjusted for 'a least one major mediating factor', such as smoking or physical health, which in some cases, attenuated the association to non-significance. This implies that the effect size reported for community settings may be an underestimate.

1.3.1.1 Community-based studies

With that in mind, Cuijpers and Smit (2002) conducted a meta-analysis of 30 community-based studies using unadjusted estimates, and found that those who were depressed had a substantially higher risk of mortality compared to those who were not depressed (RR=1.81, 95% CI: 1.58-2.07), consistent with more recent high-quality community and population-based studies (Markkula et al., 2012; Mykletun et al., 2007; White et al., 2015). Cuijpers and Smit (2002) conducted sub-group analyses by sex, age group, length of follow-up, and type of depression measure. They noted that males appeared to have a higher risk of mortality compared to females (RR=2.25, 95% CI: 1.90–2.67 and RR=1.75, 95% CI: 1.40–2.20, respectively), although the confidence intervals considerably overlapped. A handful of

other studies have demonstrated sex differences (Murphy et al., 2008; Thomson, 2011) although the large majority of the literature provides no evidence of a sex interaction (Cole, 2007; White et al., 2016; Wulsin et al., 1999). Analysis by age-group was suggestive of a stronger association between depression and mortality among those in mid-adulthood compared to those in late-adulthood. There appeared to be a higher risk of mortality in studies of those aged ≥40 years compared those aged ≥65 years (RR=2.21, 95% CI: 1.43, 3.42 and RR=1.62, 95% CI: 1.44 to 1.82, respectively), although again this difference was not statistically significant, and recent studies have shown no evidence that age acts as a moderating variable (White et al., 2016). Consistent with meta-analyses inclusive of psychiatric and medical samples (Cole, 2007; Wulsin et al., 1999), Cuijpers and Smit (2002) found that associations between depression and mortality were unaffected by the measure of depression, where studies using clinical diagnosis based on DSM criteria showed similar associations to those using self-report questionnaires. Likewise, no observable trend could be identified with respect to length of follow-up.

The results of sub-group analyses, with respect to age, sex, depression measure and length of follow-up, should be interpreted with caution however, as there was large heterogeneity in study design which makes it difficult to isolate the role of each study characteristic.

1.3.2 Long-term effects

Very few studies of depression and mortality have included a follow-up period greater than ten years (Cole, 2007; Cuijpers and Smit, 2002; Wulsin et al., 1999); however, those which have appear to illustrate a long-term effect of depression over several decades. In a Canadian community-based sample, Murphy et al., (2008) found that depression was associated with an increased rate of mortality among both men (unadjusted HR=1.8 95% CI 1.0–3.4) and women (unadjusted HR=2.1, 95% CI 1.2–3.8) over a twenty-four year follow-up. A similar trend was observed among psychiatric patients over a forty-nine year follow-up, where those who were depressed at baseline had substantially higher rates of mortality compared to the general population (Thomson, 2011). Notably, these studies used a single measure of depression; therefore it is not possible to determine whether the results reflect the long-term impact of a single episode, opposed to the accumulation of depressive symptoms over the life course.

1.3.3 Symptom severity

The majority of the literature has tested the association between affective symptoms and mortality using binary 'case' level variables to indicate the presence of depression (Cole and Dendukuri, 2003; Cuijpers and Smit, 2002; Wulsin et al., 1999). Fewer studies have explored the role of more moderate symptoms, which have also been shown to predict mortality (Cuijpers and Smit, 2002; Geerlings et al., 2002).

For instance, in the NSHD, Henderson et al., (2011) found evidence of a graded relationship between psychiatric symptoms at age 36 and mortality over a twenty year follow-up. Similar associations have been observed in the English Longitudinal Study of Ageing (ELSA), whereby White et al., (2015) demonstrated a dose-response relationship between depressive symptoms and mortality over a 9 year follow-up; notably, depressive symptoms were associated with an increased mortality risk even at low levels of symptom severity.

Sub-clinical symptoms are one of the strongest predictors of future depressive episodes (Fergusson et al., 2005a; Hardeveld et al., 2013, 2010; Kessler et al., 2003); however, no study has elucidated whether moderate symptoms in themselves increase the risk of mortality, or whether they simply capture those with an increased risk of experiencing severe symptoms that are more likely to interfere with daily functioning.

1.3.4 Depression history

1.3.4.1 Chronicity of depression

Very few studies have used repeated measures of depression to explore whether there is an accumulation effect with regards to mortality.

In a large UK population-based study of older persons, White et al., (2016) used the Center for Epidemiologic Studies Depression scale (CES-D) to assess depressive symptoms at four time-points over a period of seven years. After an average four year follow-up, they found a dose-response relationship between depressive caseness and mortality rates: compared to those who were never a case, the age and sex adjusted hazard ratios for depressive caseness at 1, 2, 3 and 4 time-points were 1.41 (95% CI 1.15–1.74), 1.80 (95% CI 1.44–2.26), 1.97 (95% CI 1.57–2.47) and 2.48 (95% CI 1.90–3.23), respectively.

Similarly, in a small community-based study of older persons in Amsterdam, Geerlings et al., (2002) used the CES-D to assess depressive symptoms at eight time points across a period of three years. Over a three-and-a-half year follow-up, they found that chronic, but

not remitting caseness predicted mortality (unadjusted HR= 2.76, 1.54-4.96, and HR=0.81, 95% CI 0.33-1.99, respectively). A similar trend has also been observed with respect to cancer incidence, where chronic depression, but not depression at a single time point, has been associated with an increased risk of developing cancer (Penninx et al., 1998a).

These studies imply that those who experience chronic depressive symptoms have a higher risk of mortality compared to those who experience remitting, or less frequent episodes; this highlights the importance of using multiple measures of affective symptoms to help distinguish between different symptom histories.

1.3.4.2 Timing of affective symptoms

Little research has been conducted which has taken into account the timing of affective symptoms, which could be a central determinant of the relationship between affective symptoms and mortality.

Whilst it may be expected that chronic affective symptoms increase the risk of mortality, there is also evidence to suggest that new-onset symptoms may be an equally good predictor of health outcomes (section 1.5.2 for further detail on the relationship between affective symptoms and physical health).

In a community based study of older persons, Penninx et al., (1998b) examined the association between depression history and mortality, and cardiovascular events. Depressive symptoms were assessed using the CES-D at three time points over a six year period; chronic depression was defined by those who were depressed twice or more, whilst new-onset depression was defined by those who were depressed immediately prior to follow-up, but not during earlier waves. Over a four-year follow-up, Penninx et al., (1998b) found that chronic and new-onset depression were equally associated with mortality (age and sex adjusted HR: 1.73, 95% CI 1.36–2.20 and HR=1.73 95% CI 1.32–2.25, respectively) . In addition, new-onset depression appeared to be a stronger predictor of cardiovascular events compared to chronic symptoms, particularly among males.

Similar findings were reported by Bruce & Leaf (1989) who showed that over a fifteen month follow-up, 'recent' affective disorder was if anything, more strongly associated with mortality compared to lifetime disorder (OR=3.0, 95%CI 1.12-7.92 and OR=1.82, 95%CI 0.78-3.29, respectively). Comparable results have also been demonstrated with respect to

studies of cancer incidence, whereby Archer et al., (2015) found that new-onset, but not chronic depression, was associated with an increased risk of cancer incidence.

These studies suggest that 'new-onset' depression could be an important risk factor for mortality, which is at odds with studies demonstrating a dose-dependent relationship (Geerlings et al., 2002; White et al., 2016). It is plausible that new-onset and chronic affective symptoms could have different pathways to mortality, which is consistent with the suggestion that early-onset and late-onset depression may have distinct aetiologies and clinical features.

Late-onset depression is usually defined by a depressive episode first occurring from ages 50-60 years onwards (Baldwin and O'brien, 2002), and is relatively rare (Kessler et al., 2005; National Centre for Social Research and Department of Health Sciences, 2009). Dysfunctional maternal relationships and family history of psychiatric disorder have been reported as strong risk factors for early-onset depression (Brodaty et al., 2001; Maier et al., 1991); however severe life stress (Van den Berg et al., 2001), somatic symptoms, and cognitive deficits (Hickie et al., 2005; Rapp et al., 2005; van Reekum et al., 1999) have all shown strong associations with late-onset depression. In addition, there is evidence to suggest that late-onset depression may encompass a sub-type of depression caused by cerebrovascular disease, known as 'vascular depression' (Alexopoulos et al., 1997; Baldwin and O'Brien, 2002; Baldwin and Tomenson, 1995); which could also help to explain why new-onset depression appeared to be a stronger predictor of cardiovascular events compared to chronic symptoms, as mentioned previously (Penninx et al., 1998b). In contrast however, some studies have shown little difference between early and late-onset depression with respect to phenomenology (Brodaty et al., 2001; Holroyd and Duryee, 1997), or vascular pathology (Janssen et al., 2006). It is possible these discrepancies could be better explained by a more detailed history of depressive symptoms.

1.3.5 Cause of death

Associations between affective symptoms and mortality have been demonstrated across many causes of death including cancer, cardiovascular disease, respiratory conditions, nervous system disorders, suicide and accidents (Chida et al., 2008; Hemingway and Marmot, 1999; Mykletun et al., 2007) (see section 1.5.1 for detail on suicide). The majority of studies have focussed on the association between depression and cancer, and

cardiovascular mortality, which are the most common causes of death in the UK (Bhatnagar et al., 2015) and globally (Lozano et al., 2013).

1.3.5.1 Cardiovascular disease

Reviews of medical, community, and population-based studies have reported that depressive symptoms increase the risk of cardiovascular disease (Rugulies, 2002; Van der Kooy et al., 2007; Wulsin and Singal, 2003) and cardiovascular mortality (Hemingway and Marmot, 1999; Lichtman et al., 2014; Nicholson et al., 2006). In a large Norwegian community-based study (n=61,349), Mykelton et al., (2007) demonstrated that depression was associated with an increased risk of death from cardiovascular disease after controlling for a range of health behaviours and somatic covariates (OR= 1.36 95%CI 1.12-1.64). Comparable results have been reported in other population-based studies (Laan et al., 2011), and among cardiovascular patients (Barth et al., 2004; Meijer et al., 2011; Van Melle et al., 2004).

1.3.5.2 Cancer

Literature exploring the association between depression and cancer has reported less consistent results. Chida et al., (2008) conducted a large review of high quality prospective studies and showed that depression was significantly associated with both increased cancer incidence (HR: 1.20, 95%CI 1.09-1.32), and mortality (HR: 1.29, 95%CI 1.11-1.52) after controlling for a wide range of mediators and confounders. Other reviews have shown more modest effects, with considerable heterogeneity among results (McGee et al., 1994; Pinquart and Duberstein, 2010; Satin et al., 2009) and concerns have also been raised over publication bias (Chida et al., 2008; Satin et al., 2009). Since cancers are not biologically homogenous it is plausible that depression may influence different types of cancer in different ways, which may help to explain mixed results.

1.3.6 Anxiety and mortality

Few studies have focussed on the extent to which anxiety symptoms influence disease and mortality. Of those which have, the reported associations are comparable to those observed for depression and mortality, which is to be expected given the high levels of co-morbidity between the two disorders (Kessler et al., 2005; National Centre for Social Research and Department of Health Sciences, 2009) (see section 1.2.4 for further discussion on comorbidity).

Among community samples of midlife and older persons, anxiety symptoms have been associated with an increased risk of all-cause, cardiovascular, and cancer mortality (Denollet et al., 2009; Eaker et al., 2005; Laan et al., 2011; Lee et al., 2006; Markkula et al., 2012; Ostir and Goodwin, 2006). However, in the NSHD, anxiety symptoms have also been identified as a protective factor against accidental mortality in early-adulthood (Lee et al., 2006), presumably as a result of lower risk-taking behaviour. Two studies have also tried to isolate the independent effects of anxiety and depression, and have found that depression, but not anxiety, was associated with an increased risk of mortality across many causes of death (Holwerda et al., 2007; Mykletun et al., 2007). Whilst these findings could potentially be explained by differences in behaviour, such as poorer help-seeking and healthcare compliance among those with depressive symptoms (DiMatteo et al., 2000; Roness et al., 2005) (discussed further in section 1.5.9.2) they could equally reflect the severity or chronicity of symptoms if, for example, anxiety disorders often precede depression (Kessler et al., 2005; Wittchen et al., 2003, 2000) (see section 1.2.4).

1.4 Summary – Affective symptoms and mortality

There is evidence of a robust association between depression and mortality among psychiatric samples, although mixed associations have been reported with respect to non-psychiatric medical and community-based samples. Null findings are in part due to studies adjusting for potential mediating factors, such as physical illness, smoking, and alcohol consumption, since positive associations are more frequently observed among unadjusted analyses or those adjusting for age and/or sex only.

Meta-analyses have shown that the association between depression and mortality does not appear to be moderated by gender, age, length of follow-up, or the measure of depression (clinical diagnosis versus self-report questionnaire); although large heterogeneity between study designs suggest that these results should be interpreted with caution.

Several studies have also shown that low or subclinical levels of depression have been associated with an increased risk of mortality, with some reporting a dose-response relationship.

Few studies have taken into account individual history of affective symptoms, or the timing of an episode. Of those which have, there is evidence to suggest an accumulation effect, whereby chronic depression is associated with a higher rate of mortality compared to those

experiencing more transient episodes. Several studies have also shown that 'new-onset', or recent depression in late-adulthood could be a distinct risk factor for mortality.

The association between affective symptoms and mortality has been observed across many different causes of death; robust associations have been demonstrated with regard to cardiovascular mortality, whilst less consistent findings have been reported with respect to cancer. Less attention has been paid to the relationship between anxiety and mortality, although similar associations have been observed to those found for depression.

1.5 Explanations for the association between affective symptoms and mortality

It is largely unclear why and how affective symptoms are associated with mortality as most studies have controlled poorly for potential mediating and confounding factors. For instance, Wulsin et al., (1999) noted that among studies investigating the relationship between depression and mortality, only 8 out of 57 controlled for more than one of smoking, alcohol abuse, ill health, or taken account of suicide.

Greater understanding of potential explanatory pathways comes from more recent community and population-based studies which have adjusted for a large range of socio-demographic, behavioural and physiological variables. In general, these studies have shown that physical illness, functional impairment, physical activity, and smoking most strongly attenuate associations between affective symptoms and mortality (Geerlings et al., 2002; Mykletun et al., 2007; Penninx et al., 1998b; White et al., 2016, 2015) and in combination with other covariates, appear to have a considerable explanatory effect (Mykletun et al., 2007; Penninx et al., 1998b; White et al., 2016, 2015). Adult cognition has also been shown to partially explain associations in some studies (White et al., 2016, 2015), although this is most likely to be an over-adjustment as depression is a risk factor for poor cognition in older people (Wilson et al., 2004, 2002). Notably, childhood cognition does not appear to attenuate associations between adult psychiatric symptoms and mortality in the NSHD (Henderson et al., 2011). Factors such as social class, education, alcohol consumption, antidepressant use and social support have weakly attenuated associations between depression and mortality in some studies, although others have found that these variables have no explanatory effect (Geerlings et al., 2002; Mykletun et al., 2007; Penninx et al., 1998b; White et al., 2016, 2015).

These findings suggest that the pathways between affective symptoms and mortality are likely to be multifactorial, but provide little insight into whether explanatory factors, such as physical illness, functional impairment or health behaviours, are potential mediators, confounders, or both. For instance, low levels of physical activity could be both a cause and consequence of affective symptoms.

Explanatory variables considered in this thesis are discussed in detail below, many of which potentially have a reciprocal relationship with affective symptoms. Variables were chosen based on their shared relationship with affective symptoms and mortality.

1.5.1 Suicide

Affective symptoms may lead directly to premature mortality through suicide. Among psychiatric and community populations, affective disorders have been identified as a strong independent risk factor for suicide (Mykletun et al., 2007; Wahlbeck et al., 2011), more so than other forms of mental disorder (Conwell et al., 2002). However, suicide appears to explain only a small fraction of the excess mortality associated with depression; for instance, suicide has been shown to account for less than 20% of deaths in psychiatric samples, and less than 1% of deaths in medical and community samples (1999). Consistent with this, several studies have shown that associations between affective symptoms and mortality hold after accounting for suicide, and violent and accidental deaths (Henderson et al., 2011; Mykletun et al., 2007; Wulsin et al., 1999).

1.5.2 Physical Health conditions

Physical health conditions are often co-morbid with depression (Moussavi et al., 2007) and have been shown to partially attenuate associations between affective symptoms and mortality (Henderson et al., 2011; Mykletun et al., 2007; White et al., 2016, 2015). There are multiple pathways by which poor physical health may explain the relationship between affective symptoms and mortality, and these pathways may also operate concurrently.

1.5.2.1 Affective symptoms cause poor physical health

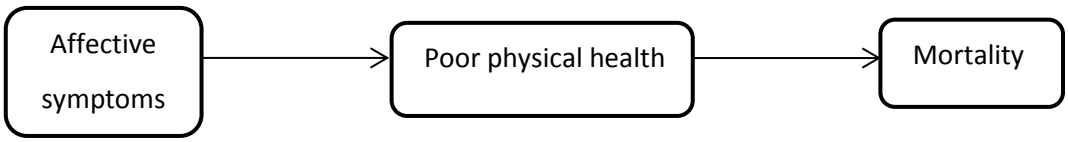

Figure 1.5.2.1 Physical health mediates the association between affective symptoms and mortality

There is evidence to suggest that affective symptoms drive poor physical health (see figure 1.5.2.1); in a nationally representative sample, Houle (2013) explored the relationship between depressive symptoms, physical health, and all-cause mortality using multiple time-points over a 16 year period. After adjustment for a range of socio-demographic and lifestyle factors, prior physical health did not appear to explain associations between depression and mortality; on the contrary, individuals who felt depressed were more likely to develop subsequent poor health and functional limitations. These findings are supported

by other studies demonstrating that depressive symptoms act as a risk factor for functional decline (Demakakos et al., 2013; Penninx et al., 2000; Stuck et al., 1999), which is turn associated with mortality (Cooper et al., 2010).

Furthermore, from a life course perspective, affective disorders tend to originate in adolescence and early-adulthood (see section 1.2.3) whilst chronic health conditions, such as diabetes, cardiovascular disease, and cancer, are relatively uncommon at younger ages. At a population level this suggests that affective symptoms are on average are more likely to precede poor physical health.

1.5.2.2 Poor physical health causes affective symptoms (reverse causality)

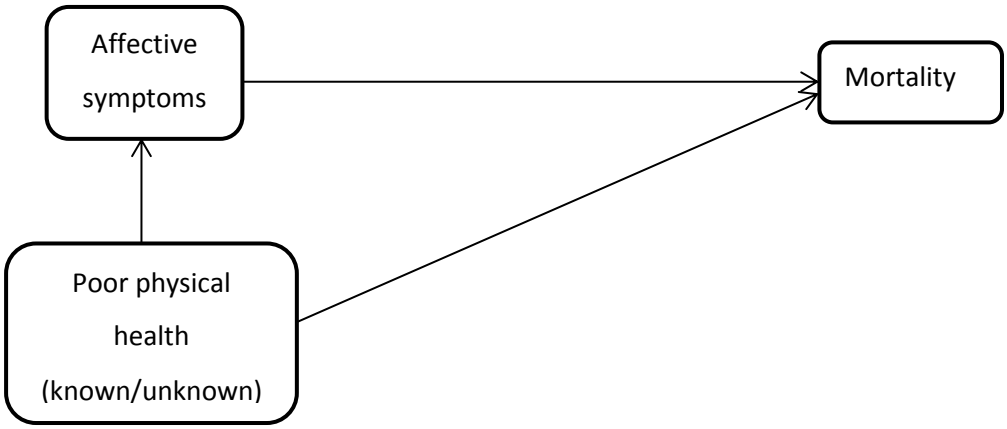

Figure 1.5.2.2 Physical health confounds the association between affective symptoms and mortality

Equally however, it is plausible that poor physical health may cause affective symptoms through psychological and direct biological processes (see figure 1.5.2.2). It is often assumed that poor physical health causes psychiatric symptoms through psychological factors, such as feelings of hopelessness, impending doom, or difficultly in maintaining social relationships or meeting personal goals due to physical limitations (Tikhonoff et al., 2016). In addition, comorbidity between depression and physical illness may also be explained by direct biological processes. For example, Dantzer et al., (2007) propose that physical illness causes the release of pro-inflammatory cytokines that act directly on the brain resulting in 'sickness behaviour', characterised by symptoms of fever, malaise, loss of appetite, pain and fatigue; it is thought that prolonged activation of the immune system

leads to the additional development of depressive symptoms in vulnerable individuals (Capuron et al., 2004; Poole et al., 2011). This is supported by observations from human and animal studies which have shown that those administered pro-inflammatory cytokines have an increased risk of developing depressive symptoms/behaviours (Dantzer et al., 2008; Elenkov et al., 2005; Schiepers et al., 2005).

It is therefore possible that physical illness may cause chronic activation of the immune system leading to inflammation and the development of depressive symptoms. This pathway could also operate with respect to underlying illnesses, such as subclinical cancer or CVD, and could potentially explain why 'new-onset' affective symptoms might increase all-cause and cardiovascular mortality risk (see section 1.3.4.2); for example, undiagnosed arteriosclerosis may elicit affective symptoms through inflammatory mechanisms prior to a cardiac event or death.

Psychological and biological pathways from poor physical health to affective symptoms are likely to be increasingly important at older ages as the prevalence of chronic disease increases.

1.5.3 The Hypothalamic Pituitary Adrenal axis, inflammation, and stress

Depression has been consistently associated with dysregulation of the Hypothalamic Pituitary Adrenal (HPA) axis and cortisol response (Burke et al., 2005; Pariante and Lightman, 2008). In turn, cortisol dysregulation has been associated with a decline in cytotoxic T-cell and natural-killer-cell activity, which is thought to influence the general immune response, and the development and progression of cancer (Reiche et al., 2004). Experimental animal studies have provided support for this theory; Filipski et al. (2002) dysregulated diurnal cortisol in mice, and found that implanted tumours grew two to three times faster than in control animals. Flattened diurnal cortisol patterns have also been reported to predict all-cause and cardiovascular mortality among British Civil Servants (Kumari et al., 2011).

Similarly, depression has been repeatedly associated with inflammation (Dantzer et al., 2007; Raison et al., 2006; Raison and Miller, 2013). Acute inflammation is an integral part of the immune response as a reaction to infection or injury; however chronic, or 'low-grade' inflammation has been associated with the development of several diseases, including atherosclerosis, diabetes, and cancer (Coussens and Werb, 2002; Hotamisligil, 2006; Libby et al., 2002). Chronic inflammation is associated with factors such as psychosocial stress

(Steptoe et al., 2007), smoking and obesity (Hamer et al., 2009; Howren et al., 2009). It is therefore possible that affective symptoms may drive inflammation by acting as a psychosocial stressor, as well as potentially influencing health behaviours such as smoking, calorie intake, and levels of physical activity (see section 1.5.4 for further discussion on health behaviours). The direction of the relationship remains controversial, however, with some studies reporting that depression precedes inflammation (Stewart et al., 2009); whilst others suggest inflammation precedes depression (Gimeno et al., 2009) – as discussed previously in section 1.5.2.2.

Notably both the inflammatory response and the HPA axis are stress sensitive systems. There is strong evidence to suggest that acute and chronic stressors predict future depressive episodes (Colman et al., 2014; Hammen, 2005) which raises the possibility that stress over the life course could be an 'upstream' driver of the association between affective symptoms and mortality (Danese et al., 2008) (for further discussion of stressors in early life see sections 1.5.8 and 1.6.3).

1.5.4 Health Behaviours

Affective symptoms have been consistently associated with detrimental health behaviours, although questions remain with regard to the direction of the relationship. For instance, the 'self-medication hypothesis' postulates that individuals may use substances such as alcohol, cigarettes, or food to medicate underlying affective symptoms (Khantzian, 1997; Singh, 2014); whilst others suggest that affective symptoms occur as a result of the adverse consequences of poor health behaviours, or substance dependence (Boden et al., 2010; Swendsen and Merikangas, 2000). Equally, it is possible that both affective symptoms and poor health behaviours are caused by common underlying genetic and/or environmental factors.

Health behaviours, such as smoking, alcohol consumption, physical activity and diet have strong and established associations with premature mortality (Doll et al., 2004; Kant et al., 2009; Knoops et al., 2004; Paffenbarger Jr et al., 1993) and affective symptoms (discussed below), which suggest that these variables could be potential explanatory factors.

1.5.4.1 Smoking

In England, those with Common Mental Disorder are one and a half times more likely to smoke than the general population (McManus et al., 2010). Several prospective studies have demonstrated that a history of depression in young adulthood is a strong predictor of

subsequent daily smoking (Breslau et al., 1998; Fuller-Thomson et al., 2013). In addition, depression may play a role in smoking maintenance; for example, smokers with major depression have been shown to be less successful in their attempts to quit compared to smokers with no history of depression (Glassman et al., 1990). In contrast however, it has also been reported that a history of smoking, particularly nicotine dependence, leads to an increased risk of depressive symptoms (Boden et al., 2010; Breslau et al., 1998), which is suggestive of a reciprocal relationship between smoking and depression.

1.5.4.2 Alcohol

Similarly, affective disorders have been associated with increased rates of alcohol consumption (Conner et al., 2009; Gratzer et al., 2004), and high comorbidity with alcohol use disorders (Kessler et al., 1997). There appears to be a bidirectional relationship between alcohol problems and depression, whereby some studies show that depression predicts alcohol abuse (Conner et al., 2009; Gilman and Abraham, 2001), whilst others suggest excessive alcohol consumption predicts subsequent depression (Gilman and Abraham, 2001). It has been proposed however, that associations between alcohol disorders and depression are best explained by a causal model whereby alcohol problems lead to an increased risk of depression, possibly through neurophysiological mechanisms (Boden and Fergusson, 2011; Fergusson et al., 2009).

1.5.4.3 Physical activity

Cross-sectional population-based studies have reported consistent associations between affective symptoms and low levels of physical activity (De Moor et al., 2008, 2006). Longitudinal studies suggest that depression may predict decreased physical activity (Roshanaei-Moghaddam et al., 2009; van Gool et al., 2003); for example, emerging depression has been associated with individuals changing from being physically active to inactive (van Gool et al., 2003). Conversely, other studies have shown that physical activity may be protective against depressive symptoms (Camacho et al., 1991; Farmer et al., 1988; Pinto Pereira et al., 2014; Strawbridge et al., 2002); however, these studies do not appear to control for depressive symptoms at baseline which means that those who had low levels of physical activity might have also been depressed, and thus more likely to experience subsequent depressive episodes (see section 1.2.3 for information on the longitudinal typology of affective symptoms).

Whilst physical activity is often used as a treatment for depression, evidence that it is a successful intervention is limited (Chalder et al., 2012; Mead et al., 2008). Longitudinal twin studies have also shown that increased physical activity does not appear to decrease affective symptoms; De Moor et al., (2008) found that among genetically identical twins, the twin who exercised more did not display fewer depressive or anxiety symptoms compared to their less active co-twin. These studies suggest that affective symptoms could be a stronger determinant of physical activity, as opposed to the reverse.

1.5.4.4 Diet

Many studies examining the association between diet and depression have focused on individual food groups or nutrients, most commonly folate, n-3 PUFA, and fish oil which have shown mixed associations with depression (Murakami and Sasaki, 2010; Sanhueza et al., 2013). Since food groups are not eaten in isolation , it has been suggested that dietary patterns may be a better predictor of disease risk (Hu, 2002); systematic reviews have provided evidence that 'healthy' and 'Mediterranean' dietary patterns are associated with a reduced risk depression (Lai et al., 2014; Quirk et al., 2013; Rahe et al., 2014), although a large proportion of these studies were cross-sectional so little is known about directionality. One prospective study using a cohort of British Civil servants attempted to assess whether diet predicted depressive symptoms over a ten-year period. After adjustment for a wide range of potential confounding factors, a strong association was found between poor diet and future risk of depression, among women only (Akbaraly et al., 2013). This study shows that the association between diet and depression persists over many years; however, it provides little evidence of directionally as the analysis did not control for depressive symptoms at baseline. For example, it is feasible that those who reported poor diet at baseline may have also been concurrently depressed.

Affective symptoms have also been associated with an overall higher calorie intake compared to individuals who were not depressed (Bonnet et al., 2005). This could also have implications for overweight and obesity, which in turn have been found to have a reciprocal relationship with depression (Luppino et al., 2010).

No study examining the association between affective symptoms and mortality appears to have controlled for diet.

1.5.5 Co-morbidity with other psychiatric disorders

It is plausible that the association between affective symptoms and mortality may be confounded by other mental disorders. As previously discussed in section 1.2.4, studies have repeatedly shown high levels of co-morbidity between different psychiatric disorders (2005; Kessler et al., 1994; Robins et al., 1991; Sartorius et al., 1996; Vollebergh et al., 2001).

Schizophrenia, bipolar disorder, and substance abuse all demonstrate strong and consistent associations with mortality (Bargagli et al., 2006; Brown, 1997; Crump et al., 2013; Markkula et al., 2012; Saha et al., 2007) and affective symptoms. For example, symptoms of schizophrenia and bipolar disorder include negative affect (Andreasen, 1982) and substance abuse is often comorbid with affective disorders (McManus et al., 2009).

Furthermore, conduct disorder in childhood has been associated with the development of affective symptoms in adulthood, in addition to a range of poor educational and social outcomes (Fergusson et al., 2005b; Richards and Abbott, 2009) which in turn is associated with premature mortality (Jokela et al., 2009; Kuh et al., 2002; Kuh and Ben-Shlomo, 2004). Externalising problems in males have also been shown to increase the risk of suicide (Geoffroy et al., 2014) and death from natural causes in later life (Maughan et al., 2014).

1.5.6 Psychotropic medication

Approximately one quarter of those with affective disorders receive treatment, mostly in the form of medication (McManus et al., 2009), which may have both deleterious and beneficial effects on health. Anxiolytics are commonly prescribed for the treatment of anxiety, but may also be prescribed for other conditions such as insomnia and alcohol withdrawal. Likewise, anti-depressants are by definition used to treat depression, but may also be prescribed for chronic anxiety, post-traumatic stress, substance abuse, eating disorders, and chronic or neuropathic pain (British Medical Association & Pharmaceutical Society of Great Britain, 2002).

Few studies examining the relationship between affective symptom and mortality have controlled for antidepressant use, and none appear to have controlled for anxiolytic use. Among community-based studies, Penninx et al., (1998b) and White et al., (2016, 2015) found that controlling for antidepressant use minimally altered associations between depressive symptoms and mortality; although no differentiation was made between different types of antidepressant medication.

1.5.6.1 Antidepressants

All major types of antidepressant medication are associated with an elevated risk of hypertension (Grossman and Messerli, 2012; Licht et al., 2009; Thase, 1998). Tricyclic antidepressants are particularly detrimental to health and have been shown to increase the risk of cardiovascular disease (Hamer et al., 2010b) and accelerate the growth of existing tumours in rats and mice (Marx, 1992). There is also suggestive evidence of association between tricyclic antidepressants and raised inflammation (Hamer et al., 2011a; Vogelzangs et al., 2012) and cancer progression (Sharpe et al., 2002; Sternbach, 2003). In contrast, selective serotonin reuptake inhibitors (SSRIs) have been associated with lower levels of inflammation in men (Vogelzangs et al., 2012) and are shown to be protective against cardiovascular events and mortality (Sauer et al., 2001; Taylor et al., 2005; Vogelzangs et al., 2012) possibly due to the influence of SSRIs on platelet aggregation (Serebruany et al., 2003). Equally however, a systematic review of randomised trials demonstrated that depressed patients taking SSRIs were more than twice as likely to attempt suicide than those taking placebo (Fergusson et al., 2005).

1.5.6.2 Anxiolytics

Several studies have shown that short-term anxiolytic use is associated with a blunted response to adrenocorticotropic hormone (ACTH), a reduction in cortisol levels, and lower systolic blood pressure (Fries et al., 2006; Lopez et al., 1990); all of which are suggestive of potential health benefits. However, long-term use has been associated with tolerance, dependence and withdrawal problems (Ashton, 2012) in addition to an increased risk of mortality (Parsaik et al., 2015; Weich et al., 2014).

Weich et al., (2014) used patient records to demonstrate a strong dose-response relationship between anxiolytic medication and mortality; over a seven year follow-up, those who received over ninety daily-doses of benzodiazepines over a three year period had over three times the risk of mortality compared to those not taking anxiolytics, after adjustment for physical health problems, psychiatric disorders, other prescription medications, smoking and alcohol use (adjusted HR=3.32, 95% CI: 2.83-3.89). In contrast, Hausken et al., (2007) found that associations between anxiolytic or hypnotic medication and mortality were no longer statistically significant after controlling for life-style and socioeconomic factors; however, participants were asked about their drug use in the last month only, which could help explain this discrepancy.

1.5.7 Social support

Holt-Lunstad et al., (2010) conducted a large meta-analysis of 148 studies which revealed a robust inverse association between social relationships and mortality, consistent across age, sex, initial health status, cause of death, and follow-up period. The strongest associations were found with regard to measures of social integration (OR = 1.91; 95% CI 1.63 to 2.23) which reflect the degree to which an individual is integrated in structural social networks.

It is plausible that depressive symptoms may be driving this association as depression may lead to the erosion of social networks, particularly peer support (Stice et al., 2004). Equally, it is possible that poor social relationships may increase vulnerability to depression. For example, in community-based population cohort, Glass et al., (2006) found that among those free from depression at baseline, social engagement was protective against developing future depressive symptoms. In addition, there is also evidence to suggest that social support may modify the effect of affective symptoms on mortality. Among myocardial infarction patients, Frasure-Smith et al., (2000) found that very high levels of social support buffered the effect of depression on mortality.

Few community-based studies investigating the relationship between affective symptoms and mortality appear to have adjusted for measures of social support. White et al., (2016, 2015) adjusted for 'living alone' which resulted in a small attenuation, whilst Houle et al., (2013) adjusted for social integration and found that this did not explain the relationship between depression and mortality. No studies appear to have tested for moderating effects.

1.5.8 Adverse Childhood Experiences

This thesis defines Adverse Childhood Experiences (ACE) as a set of traumatic and stressful psychosocial conditions beyond the child's control: "…events or conditions causing chronic stress responses in the child's immediate environment. These include notions of maltreatment and deviation from societal norms, where possible to be distinguished from conditions in the socioeconomic and material environment" (Kelly-Irving et al., 2013, p. 2).

Biological embedding models of childhood adversity propose that exposure to stress during sensitive periods in childhood may lead to alterations in various biological systems, which may influence response to subsequent stressors, and in turn influence behaviour, and health, over the life course (Hertzman, 1999). This is supported by studies showing that

childhood adversity is associated with an abnormal stress response (Heim et al., 2000), dysregulation of the HPA axis (Heim et al., 2008, 2000; Power et al., 2012), and raised levels of C-reactive protein (CRP) in mid-adulthood (Danese et al., 2007; Lacey et al., 2013). Equally, studies have demonstrated that ACE are associated with lower educational attainment (Lacey et al., 2013), lower levels social support in adulthood (Fagundes et al., 2011), and adoption of high risk health behaviours (Miller et al., 2011). There is limited evidence however as to the extent to which mental health may mediate associations between ACE and social and biological outcomes (Danese et al., 2007; Lacey et al., 2013).

Associations between affective symptoms and mortality could potentially be explained by ACE as they appear to predict both mental disorder and mortality in later life.

1.5.8.1 ACE and Psychological Outcomes

Prospective studies have demonstrated conclusive evidence of an association between ACE and the development of child and adolescent psychopathology (Grant et al., 2004). There is less literature on adult psychopathology, although similar findings have been reported with respect to physical and sexual abuse, neglect, bullying, and parental divorce (Clark et al., 2010; Collishaw et al., 2007; Evans-Lacko et al., 2016; Kim et al., 2013; Rodgers et al., 1997; Widom et al., 2007). Studies incorporating retrospective measures have also reported strong dose-response relationships between the number of adversities and the risk of adult psychopathology (Chapman et al., 2004; Clark et al., 2010; Danese et al., 2009; Schilling et al., 2008). Further discussion of ACE in the NSHD can be found in section 1.6.3.

1.5.8.2 ACE and mortality

Few studies have assessed the relationship between ACE and premature mortality. Retrospective measures of childhood adversity have been associated with mortality across all major causes of death (Brown et al., 2009). Only two prospective population-based studies have examined this association. Geoffroy et al., (2014) found a graded association between the number of childhood emotional adversities and the risk of suicide over a fifty-year follow-up. Similarly, Kelly-Irving et al., (2013) found that, in men, those with two or more ACE had an increased risk of premature death, whist a stronger and graded relationship was observed in women. Notably, these associations were largely unexplained by adjusting for affective symptoms in adulthood, and affective symptoms remained a significant predictor of death in women. This study implies that affective symptoms do not

mediate the associations between ACE and mortality, and that ACE and affective symptoms may have independent pathways to mortality.

1.5.9 Other potential explanatory factors

1.5.9.1 Genetics

It is plausible that genetics factors could confound or moderate associations between affective symptoms and mortality. Studies have shown that the effect of stressful-life events on depression appeared to be moderated by a variant of the serotonin transporter gene (Caspi et al., 2003; Kendler et al., 2005), although this finding has not been replicated in other studies (Risch et al., 2009). In addition, a review by McCaffery et al., (2006) concluded that the association between depression and coronary artery disease may be partially attributable to a common genetic vulnerability. Twin and family studies have also shown that depression and anxiety disorders have a considerable genetic component; however a much larger proportion of the variance has been shown to be due to non-shared environmental effects (Hettema et al., 2001; Polderman et al., 2015; Sullivan et al., 2014) which will be the focus of this thesis.

1.5.9.2 Access to Healthcare

Inferior healthcare received by those with psychiatric disorder may partially explain the mortality gap between those with affective disorders and the general population. Mitchell et al., (2009) conducted a systematic review of 31 studies assessing the quality of medical care received by those with psychiatric disorder compared to the general population. They found that those with psychiatric disorders, including depression, were more likely to seek help and utilise healthcare services, yet were less likely to receive adequate healthcare, with regard to general medicine, diabetes, cardiovascular and cancer care.

There are several speculative explanations as to why those with psychiatric disorders appear to receive poor quality medical care. One possibility is non-compliance; for example, a meta-analysis by DiMatteo et al., (2000) showed that patients with depression had over three times the odds of being non-compliant with medical treatment recommendations compared to non-depressed patients. Similarly, among patients with diabetes, depression was associated with lower adherence to hypoglycaemic, antihypertensive, and lipid-lowering medications (Lin et al., 2004). Equally, it is plausible that physical disease is more likely to go unrecognised in those with psychiatric disorder due to poor communication with health care providers (Miller et al., 2014) or ‘diagnostic

overshadowing' (Jones et al., 2008), whereby health providers may incorrectly attribute somatic complaints to psychiatric problems.

Whilst non-compliance, adherence to medication, and the quality of relationship with health care providers are potentially important explanatory factors, they are not possible to measure directly using the NSHD data and are therefore not examined in this thesis.

1.6 Affective symptoms and mortality in the National Survey of Health and Development (1946 British Birth Cohort)

1.6.1 Psychiatric symptoms and mortality

Henderson et al., (2011) used data from the NSHD to explore the association between psychiatric symptoms in mid-life and premature mortality. Psychiatric symptoms were assessed at age 36 using the Present-State-Examination (PSE) and study members were followed up to age 60 years. After adjusting for a range of potential mediators and confounders, they found that both 'mild' and 'moderate/severe' psychiatric symptoms increased the risk of premature mortality (HR=1.77, 95% CI 1.20-2.61, and HR=1.84, 95% CI, 1.22-2.78, respectively). The results were not explained by suicides or violent causes of death, but appeared to be partially accounted for by smoking and physical health status; although the residual association remained statistically significant. Factors such as childhood and adult social class, educational attainment, and childhood cognition did little to attenuate the relationship. Notably, the observed associations cannot be attributed to affective symptoms alone as the PSE assesses a range of psychiatric symptoms, including those of mania, psychosis, and substance abuse.

Lee et al., (2006) used the NSHD to test the association between adolescent anxiety, and accidental and non-accidental mortality up to age 50 years. High adolescent anxiety was associated with a lower risk of accidental death prior to age twenty-five, but with a higher risk of non-accidental mortality in later life. The results suggest that anxiety could act as a protective trait during early adulthood; however the results were adjusted for sex only, and the measure of anxiety was not robust – anxiety was assessed using a single teacher-rated question at ages 13 and 15, asking whether the child was 'apprehensive, worried or fearful' compared to other children.

Neeleman et al., (1998) also demonstrated that teacher-rated emotional and behavioural problems at age 13 and 15 years, including conduct problems, habit/tics, and aggression, were all associated with an increased risk of suicide and death from natural causes over a thirty-four year follow-up. Similarly, adolescent conduct problems were associated with premature cardiovascular mortality among men, and all-cause and cancer mortality among women (Maughan et al., 2014).

1.6.2 Risk factors for mortality

Associations have been demonstrated in NSHD between mortality and stunted childhood growth (Ong et al., 2013), high and low body-mass-index (BMI) in early adulthood (Strand et al., 2012), and poor socio-economic conditions in childhood and early adulthood (Kuh et al., 2002). Low childhood cognitive ability has been shown to predict premature mortality in men but not women; although associations were largely attenuated after adjustment for education and adult socioeconomic position, suggesting that cumulative exposure to poor socioeconomic conditions is likely to explain this effect (Kuh et al., 2004).

Affective symptoms have also been associated with several risk factors for mortality. For instance, among women, affective symptoms were associated with higher BMI in adulthood; whilst males demonstrated a lower BMI compared to those with no symptoms (Gaysina et al., 2011). In addition, severe emotional problems in adolescence have also been associated with lower earnings, twice the odds of having no educational qualifications, and with increased odds of never marrying (Richards and Abbott, 2009).

1.6.3 Early life risk factors for psychiatric disorder and affective symptoms

A strong risk factor for affective symptoms in adulthood is affective symptoms in adolescence. Colman et al., (2007b) found that approximately 70% of adolescents who had emotional problems in adolescence also had problems at ages 36, 43, or 53 (see section 1.2.3 for further discussion of longitudinal typologies).

Rodgers (1990) examined the association between early childhood environment and psychiatric disorder at age 36. They found the highest rates of psychiatric disorder in those who experienced multiple adversities, and this association was stronger in women. For men, the prevalence of psychiatric disorder in the most disadvantaged group (16.7%) was five times that in the least disadvantaged group. For women, the prevalence in the most disadvantaged group (32.3%) was seven times that in the least disadvantaged. Similarly, parental divorce has been shown to be a risk factor for depression in women, but not among men (Rodgers et al., 1997). Notably, separation as a result of parental death demonstrated no association with adult affective symptoms (Rodgers et al., 1997) suggesting that the increased risk attributed to divorce is perhaps due to the effects of interpersonal conflict and hostility, opposed to the separation itself (Rodgers, 1994).

Rodgers (1990) additionally explored the impact of childhood material adversity, and found that among women, overcrowding, housing tenure, and low social-class, predicted a greater number of psychiatric symptoms. However, an overall index based on material home conditions was unrelated to the development of psychiatric symptoms. Chronic physical illness in childhood has also been associated with a higher likelihood of psychological distress in early adulthood, which was not explained by income (Pless et al., 1989).

Less research has been conducted into adult risk factors for affective symptoms, although it has been demonstrated that own divorce or separation in adulthood is associated with an increased risk of anxiety, depression, and alcohol abuse (Richards et al., 1997). Consistent with this, Colman et al., (2014) found that stressful life events in adulthood, including death of a loved one, an employment crisis, and being assaulted, were stronger predictors of depression than adolescent mental disorder.

1.7 Summary: Pathways and directionality

There is evidence to suggest that physical health, smoking, alcohol problems, diet, physical activity, and social support may all potentially have bidirectional associations with affective symptoms, which means they could be 'upstream' on the causal pathway, confound or mediate associations between affective symptoms and mortality.

Few studies appear to have given consideration to the timing or history of affective symptoms, which could help elucidate explanatory pathways. For instance, an affective symptom episode first occurring in late-adulthood is more likely to be a consequence of factors such as chronic smoking, poor health, and low levels of physical activity, opposed to a cause. Conversely, enduring affective symptoms first occurring in adolescence are potentially more likely to play a role in the maintenance and development of detrimental health behaviours over the life course, in addition to influencing factors such as educational attainment, and employment.

Directionality is easier to ascertain for other explanatory variables. Anxiolytic and antidepressant medication may mediate the association between affective symptoms and mortality, whilst suicide represents a direct pathway between affective symptoms and mortality.

There is strong evidence to suggest that ACE and stressful-life events are associated with an increased risk of depression, which suggests that these factors could be 'upstream' on the causal pathway, and in addition some studies imply that ACE and affective symptoms may have independent pathways to mortality.

Other factors such as genetics and the quality of health care may also be important explanatory factors, but are beyond the scope of this thesis.

1.8 Conceptual framework

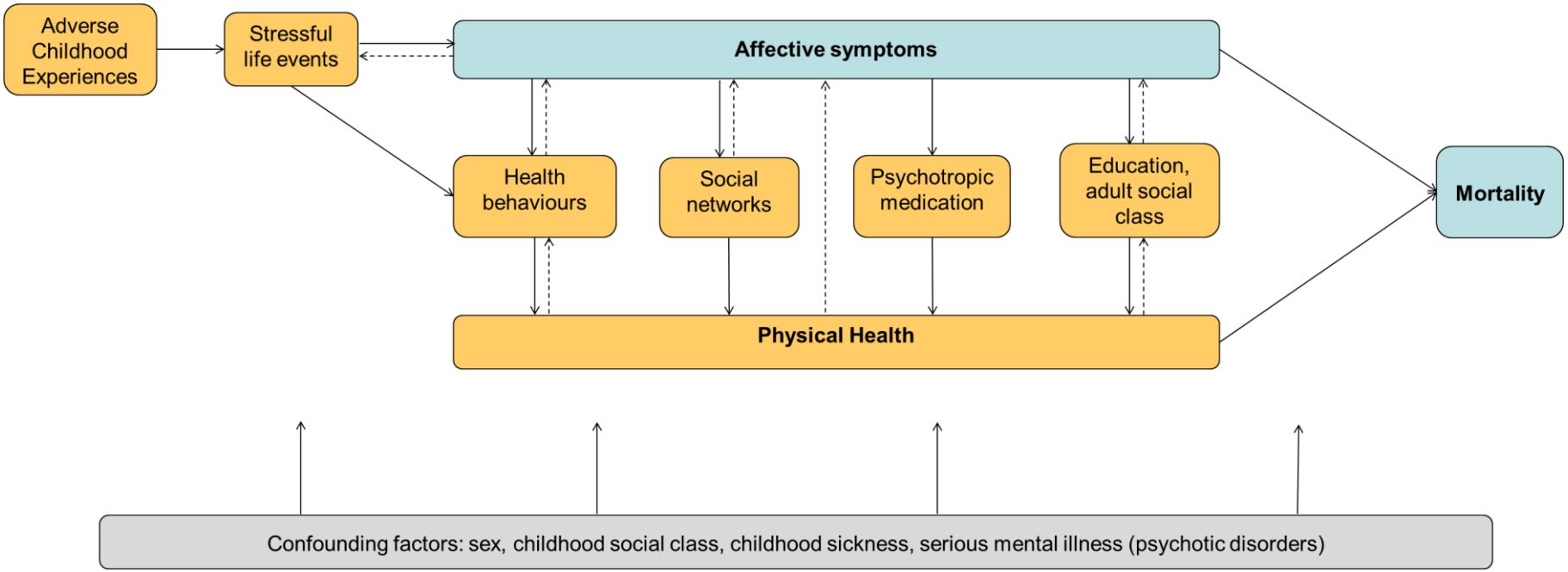

Figure 1.8 Conceptual framework

Figure 1.8 shows a conceptual framework which demonstrates potential pathways between affective symptoms and mortality based the explanatory variables considered in this thesis.

The main exposure and outcomes are represented by the blue boxes, potential confounders are shown in grey, and the orange boxes represent variables that could be mediators, confounders, or up-stream factors depending on the direction of the association. Adverse childhood experiences (ACE) and stressful life events are presented as a potential 'upstream' cause of affective symptoms (for clarity, pathways between ACE, stressful life events and mortality have been omitted). There is a direct association between affective symptoms and mortality which denotes suicide, whilst all other solid arrows between affective symptoms and mortality represent mediating pathways whereby affective symptoms influence health behaviours, social networks, and psychotropic medication use, educational attainment and adult social class, which in turn impact physical health and mortality. The dashed arrows represent variables that may also have a bidirectional relationship with affective symptoms; for instance, affective symptoms could also be determined by physical health, social networks, education, and health behaviours. It is therefore important to consider the timing of affective symptoms when interpreting the framework. For instance, factors such as education, health behaviours, social networks, and physical health are more likely to act as mediators if affective symptoms originate in adolescence, but are more likely to be 'upstream' determinants if affective symptoms first occur in late-adulthood.

1.9 Rationale

Associations between affective symptoms and mortality have been demonstrated among psychiatric, medical, and community based samples, and across many causes of death; however, nearly all studies have relied on a single measure of depression in mid-life or older adulthood, which makes difficult to make inferences about the characteristics of the association. For instance, several studies have demonstrated that sub-clinical depressive symptoms predict mortality; however a single measure of affective symptoms cannot distinguish whether moderate symptoms in themselves raise the risk of mortality, or whether they simply reflect an increased propensity for experiencing severe episodes as a result of an underlying disorder. Likewise, very few prospective studies have used repeated measures of affective symptoms, and of those which have, symptoms have been assessed

among older persons over a maximum period of seven years. Whilst these studies provide insight into potential accumulation effects, they cannot capture individual history of affective symptoms and therefore cannot ascertain, for example, whether the associations observed in adulthood are driven by affective disorders emerging in adolescence. Very little is known about the relationship between affective symptoms occurring in adolescence or early-adulthood and mortality among community-based samples. Furthermore, almost no studies have taken into account the timing of affective symptoms, which could help determine potential explanatory mechanisms; for example, early and late-onset affective symptoms are likely to have distinct pathways to mortality (see section 1.3.4.2). Finally, there is very weak understanding of possible explanatory pathways between affective symptoms and mortality. Very few studies have controlled for a comprehensive range of potential mediators or confounders. Of those which have, factors relating to physical health status and health behaviours appear to most strongly attenuate associations (see section 1.5 for discussion); however the directionality of associations is unclear.

This thesis aims to address these current gaps in the literature by building on the work of Lee et al., (2006) and Henderson et al., (2011) who previously demonstrated an association in the NSHD between premature mortality and anxiety and psychiatric symptoms, respectively. Uniquely, the NSHD data has measures of affective symptoms spanning from adolescence to late-adulthood, which will allow the association between affective symptoms and mortality to be investigated with respect to the timing, severity, and chronicity of symptoms across the life course. The NSHD also has excellent data on a wide range of potential explanatory variables, such as 'lifetime' measures (obtained from multiple time-points) of physical health status, physical activity, and smoking. Additionally, the data includes clinical and behavioural factors that no previous study has controlled for, such as diet, anxiolytic medication use, and lung function. This thesis is therefore positioned to enrich the current literature by examining the characteristics of the association between affective symptoms and mortality over the life course, in addition to providing a greater understanding of potential explanatory pathways.

2. AIMS AND OBJECTIVES

2.1 Aim

The overall aim of this thesis is firstly to investigate the nature of the association between affective symptoms and mortality over the life course, and secondly to investigate the potential explanatory role of a range of social, behavioural and physiological factors.

2.2 Objective 1

To investigate the association between affective symptoms and mortality with respect to:
1.1. Age (ages 13-15, 36, 43, and 53 years)

1.2. Symptom severity (mild, moderate, severe)

1.3. Symptom type (anxiety, depressive)

2.2.1 Hypotheses relating to objective 1

1.1. Affective symptoms will be associated with mortality at all ages across the life course (ages 13-15, 36, 43, and 53 years)

1.2. Severe affective symptoms will be more strongly associated with mortality compared to moderate/mild symptoms

1.3. Both anxiety and depressive symptoms will be equally predictive of mortality

2.3 Objective 2

To investigate the association between lifetime affective caseness and mortality with respect to:

2.1. Affective caseness accumulation

2.2. Affective case history (adolescent-only, new-onset, intermittent, and chronic caseness)

2.3. Cause-specific mortality (cancer, cardiovascular, externalising, other)

2.3.1 Hypotheses relating to objective 2

2.1. There will be a dose-response relationship between affective case accumulation and mortality

2.2. New-onset symptoms will predict mortality, indicative of reverse causality with poor physical health.

2.3. Affective caseness will be associated with mortality across all causes of death, particularly cardiovascular deaths.

2.4 Objective 3

To investigate to what extent the relationship between lifetime affective caseness and mortality can be explained by the following factors:

3.1. Physical health status (clinical and self-reported)

3.2. Health behaviours (smoking, alcohol consumption, physical activity, and diet)

3.3. Psychotropic medication use (anxiolytics, antidepressants)

3.4. Social networks (marriage, friends)

3.5. Stressful life events

3.6. Adverse childhood experiences (parental divorce, parental abuse, neglect)

2.4.1 Hypothesis relating to objective 3

3.0 Physical health status, health behaviours, psychotropic medication use, social networks, stressful life events, and adverse childhood experiences will all partially explain the association between lifetime affective caseness and mortality.

Psychotropic medication will mediate the association between affective caseness and mortality; all other factors could mediate and/or confound associations.

3. DATA AND METHODS

3.1 Chapter overview

This chapter begins by introducing the data source used in this thesis – the MRC National Survey of Health and Development (NSHD), also known as the 1946 British Birth Cohort Study. The NSHD is described with regard to the specific objectives of this thesis, and issues relating to attrition and the representativeness of the data are discussed. A detailed history of the NSHD has been outlined previously in other papers (Kuh et al., 2011; Wadsworth et al., 2006; Wadsworth, 1987; Wadsworth and Kuh, 1997). The chapter then presents methodologies that are shared between analyses, including a description of the main exposures (affective symptoms), outcome (mortality), and covariate variables, including details of how they were derived.

3.2 Introduction to the MRC National Survey of Health and Development

The MRC National Survey of Health and Development (NSHD) is the oldest British birth cohort study. The study was based on a national maternity survey conducted in 1946 and was originally designed to investigate falling fertility rates and the efficacy of midwifery services (Wadsworth et al., 2006). Of 16,695 births recorded in England, Scotland and Wales during one week in March 1946, a socially stratified sample of 5,362 (2,547 female, 2815 male) singleton births occurring within marriage were selected for follow-up, consisting of all births from women with husbands in non-manual and agricultural employment, and a random selection of one in four births to women with husbands in manual employment. The sample excluded those from local authorities who refused to participate (n=1279), multiple births (n=180) and births outside marriage (n=672).

The cohort has been followed-up 23 times at regular intervals across the lifecourse, most recently at age 69, with further data collections planned. A mixture of teacher and parental reports, postal questionnaires, trained interviewers, and a clinic visit has been used to collect data on a wide range of psychological, physical, behavioural, and social factors (Kuh et al., 2011). In the last fifty years the study has helped to inform public policy in areas relating to maternal care, socio-economic differences in educational attainment, employment, and more recently healthy ageing (Kuh et al., 2013; Wadsworth, 1987; Wadsworth and Kuh, 1997).

The NSHD is particularly suited to test the research hypotheses for this thesis, as it is unique in containing prospective measures of affective symptoms from adolescence to adulthood, in addition to extensive data on potential mediators and confounders (see section 1.9 for rationale).

The study is also very ethnically homogenous, therefore cultural differences in the presentation and diagnosis of mental disorder (Fernando, 2010) are unlikely to influence the findings presented in this thesis.

3.3 Attrition and representativeness of the cohort

Table 7.1 Response rates in the MRC National Survey of Health and Development

Year	Age	Respondent	Contact	% Target
1946-50	0-4	Mother	4695	95
1951-61	5-15	Mother & Study Member	4307	89
1962-81	16-35	Study Member	3538	78
1982	36	Study Member	3322	86
1989	43	Study Member	3262	87
1999	53	Study Member	3035	83
2006-10	60-64	Study Member	2661	84

Source: Stafford et al., (2013) and Wadsworth et al., (2006).

Loss to follow-up is often systematic and can act to strengthen or weaken association estimates. Despite attrition through death, emigration and refusal, table 1 shows that response rates have been relatively high throughout the study, which helps to minimise selection bias.

Previous studies have compared social class weighted NSHD data to age-matched census data and demonstrated that the NSHD was largely representative of the general population at ages 43, 53, and 60-64 years (Stafford et al., 2013; Wadsworth et al., 2003) – allowing for various waves of immigration and some study member emigration since the study's inception, and the above initial exclusion criteria. At age 60-64 years, Stafford et al., (2013) demonstrated that NSHD study members had a similar gender and social class distribution to the 2001 English census data, but were more likely to be employed, married, own their own home, and less likely to have a lifelong limiting illness. A weighting factor was used in the aforementioned studies to improve the representativeness of the sample. The NSHD

weight is based solely on study members' social class at birth which was designed to account for the initial over-sampling of those whose fathers were from non-manual and agricultural occupations; however, it does not account for other variables that have been associated with non-response over the course of the study, such as lower educational attainment, lower childhood cognition, lifelong smoking, adult manual social class, and obesity (Stafford et al., 2013; Wadsworth et al., 2003). This thesis did not use the NSHD weight but instead adjusted analyses for variables associated non-response and sampling stratification; this allows the role of each variable to be better understood with respect to their relationship with affective symptoms and mortality.

There is little evidence to suggest that the association between affective symptoms and mortality is biased by attrition (Graaf et al., 2000). It has been demonstrated that mental health profiles across several sweeps of the NSHD, did not predict response in subsequent waves (Stafford et al., 2013). Likewise, NSHD mortality data was obtained from National Health Service Central Registry information, which is unrelated to loss to follow-up; it has also been shown that mortality rates among study members were equivalent to the national population from the first year of life onwards (Wadsworth et al., 2003).

3.4 Main Exposures: Affective symptoms at ages 13-15, 36, 43 and 53

Measures of affective symptoms were available at ages 13, 15, 36, 43 and 53 years.

3.4.1 Age 13/15: Teacher-rated questionnaire

Affective symptoms were assessed by teachers using a forerunner of the Rutter B questionnaire (Rutter, 1967). At ages 13 and 15, teachers were asked to rate the study member's behaviour compared to other children in the class using a three category response scale – more than, the same, or less than other children. The questionnaires had been previously subjected to exploratory factor analysis using probit models for categorical outcomes in the statistical package Mplus 6.1 which identified three distinct factors relating to emotional problems, externalising behaviour (conduct problems) and self-organisation (Xu et al., 2013). Ten-items loaded onto emotional problems, which were "Anxious", "Always tired and washed-out", "frightened of rough games", "extremely fearful", "avoids attention", "usually gloomy and sad", "timid child", "unable to make friends", "diffident about competing", and "unduly miserable or worried about criticism"

(see Appendix A for original questions). Factor scores as derived by Xu et al., (2013), were standardised at age 13 and 15 and then summed to create a single measure of adolescent affective symptoms.

3.4.2 Age 36: Present-State-Examination (PSE): Affective symptom factor score

At age 36 affective symptoms were assessed using the short-form of the Present-State-Examination (PSE) (Wing et al., 1978, 1974), which was administered by trained nurses to study members in their home. The PSE is a semi-structured clinical interview designed to assess the frequency and severity of psychiatric symptoms in the preceding month, and has shown good reliability between psychiatrists and non-psychiatrists if given appropriate training (Wing et al., 1977). The PSE covers symptoms of common mental disorder, in addition to those related to psychotic disorders and substance abuse. Each item is scored on a 3-point scale; symptom not present (0); moderate severity or frequency of symptom (1); severe and frequent symptom (2). The PSE is usually scored using a computer algorithm called 'Catego' which produces a severity index as well as specific ICD-9 diagnoses (Wing et al., 1978, 1974).

In order to isolate the influence of affective symptoms only, items relating to anxiety and depressive symptoms were extracted from the PSE questionnaire based on the Diagnostic and Statistical Manuals III-IV (American Psychiatric Association, 1994, 1980), and ICD-9 (World Health Organization, 1998) definitions. For the purpose of this thesis, exploratory factor analysis was used to identify twenty questions which loaded strongly onto a single predominant factor, and that had good internal consistency (Cronbach's alpha 0.83). Confirmatory factor analysis was then conducted using MPlus to create a factor score for affective symptoms at age 36. Details of how this score was derived can be found below.

3.4.2.1 Deriving a factor score for affective symptoms at age 36

Initially, twenty-five items representing symptoms of anxiety and depression were extracted from the Present-State-Examination questionnaire based on DSM III-IV and ICD definitions (American Psychiatric Association, 1994, 1980; World Health Organization, 1998). Exploratory factor analysis identified a single predominant factor, of which five questions loaded poorly and were dropped from further analyses. These questions related to suicidal plans or acts, loss of appetite, self-consciousness in public, feeling physically ill, and worrying over physical health. It is possible that suicidal plans and poor appetite had

low loadings because these items asked about events over a longer time period compared to other items in the scale; for example, 'did you ever feel like ending it all?', and 'have you lost any weight in the past three months?'. In addition, it is possible that items relating to poor appetite, worrying over physical health, and feeling physically ill, more strongly tapped poor physical health than poor mental health.

The remaining twenty items demonstrated good internal consistency (Cronbach's $\alpha = 0.83$) (see Appendix B for list of items). The presence of a single underlying factor representing affective symptoms was tested by confirmatory factor analysis (CFA), using MPlus. The model demonstrated good fit (RMSEA = 0.03; CFI = 0.96; TLI = 0.96), and all items loaded strongly onto the latent factor ($p<0.001$). Factor scores were generated from all available data; however only those who were complete on all items, or missing a single item, were included in subsequent analyses. This approach retained an extra 223 study members compared to simply summing those who had complete data on all PSE items.

PSE total score vs. PSE factor score

Sensitivity analysis was conducted to establish whether the twenty-item PSE total score and PSE factor score would produce different results. Descriptive analyses showed that 95% of those who were an affective case using the PSE total score were also a case using the factor score (caseness was defined by those in the top 16%). Cox regression demonstrated that the association between mortality and severe affective symptoms was almost identical for the PSE total score and PSE factor score; the sex adjusted hazard ratio for severe affective symptoms was 1.25 (95% CI 0.93-1.67), and 1.25 (95% CI 0.94-1.66), respectively. The PSE factor score was used, opposed to the total score, as this approach led to fewer missing data.

Inclusion vs. exclusion of suicide item

Those reporting that they had considered or attempted suicide accounted for only 1.2% of the sample; however, a sensitivity analysis was conducted to ensure that excluding suicide from the twenty-item PSE total score did not bias results. Cox regression showed that there was no evidence that inclusion of suicide strengthened the association between affective symptoms and mortality; the sex adjusted hazard ratio for severe symptoms was 1.25 (95% CI 0.93-1.67) if excluding suicide, compared to 1.22 (95% CI 0.91, 1.63) if including suicide.

3.4.3 Age 43: The Psychiatric Symptom Frequency Scale

Affective symptoms at age 43 were measured by The Psychiatric Symptom Frequency scale (PSF), which was based largely on questions from the Present-State-Examination. The PSF is an 18-item questionnaire administered by trained interviewer, which assesses the frequency of anxiety and depressive symptoms in the preceding year (Lindelow et al., 1997). Item response ranges from 0 (never in the last year) to 5 (every day in the last year). PSF scores are calculated by adding the 18 items of the scale, allowing the total score to range from 0 to 90 (see Appendix C for list of items). The scale was specifically developed for NSHD to evaluate symptoms over a longer period of time, which makes it less susceptible to floor effects, in addition to providing better discrimination between occasional and persistent symptoms (Lindelow et al., 1997).

The scale has previously been subjected to exploratory factor analysis which revealed a single predominant factor incorporating symptoms of depression and anxiety, with high internal consistency (Cronbach's alpha = 0.88) (Lindelow et al., 1997). Receiver operating curve (ROC) analyses demonstrated that high scores on the PSF were strongly associated with suicidal ideation, and reports of contact with a health professional and use of medication for "nervous or emotional trouble or depression". The analysis suggested cut offs of 13/14 or 22/23, depending on whether the scale was to be used for screening or defining a population at high risk of mental disorder, respectively (Lindelow et al., 1997). However, the PSF has not been validated in other studies, and as such varying thresholds have been used to match the prevalence of mental disorder obtained from more widely used and validated measures (Paykel et al., 2001; van Os et al., 1997).

3.4.4 Age 53: The 28-item General Health Questionnaire

The General Health Questionnaire (GHQ) is a self-reported screening questionnaire which assesses anxiety and depressive symptoms in the preceding four weeks, and is commonly used as a screening tool for psychiatric disorder in both primary care and community settings (Goldberg et al., 1976).

Affective symptoms at age 53 were measured using the 28-item version of this (GHQ-28), which was derived by factor analysis from the original 60-item GHQ. The GHQ-28 consists of four sub-scales: somatic symptoms, anxiety and insomnia, social dysfunction and severe depression, which were found to be correlated suggesting the presence of a single underlying factor (Goldberg and Hillier, 1979) (see Appendix D for list of items).

Each item is rated on a four-point scale with answers ranging from 'better/healthier than normal', 'same as usual', 'worse/more than usual' to 'much worse/more than usual'. The GHQ can be scored in different ways depending on the research question. The standard 'GHQ-scoring' method scores each item 0-0-1-1 and is recommended as the best method for identifying 'caseness' (Goldberg et al., 1997; Goldberg and Hillier, 1979). In contrast the Likert method scores each item 0-1-2-3, and is recommend when assessing the severity of affective symptoms as a continuous measure as it produces a normal distribution (Goldberg et al., 1997; Goldberg and Hillier, 1979). The total GHQ score is the sum of each item, which ranges from 0-28 for the GHQ-scoring method (0-0-1-1), and from 0-80 for the Likert method (0-1-2-3).

The overall validity and reliability of the 28-item GHQ has shown to be very high for both the GHQ-scoring and Likert scoring methods (Goldberg et al., 1997; Goldberg and Hillier, 1979; Lobo et al., 1986), and the original factor structure has been replicated in later studies and across cultures (Gibbons et al., 2004; Werneke et al., 2000).

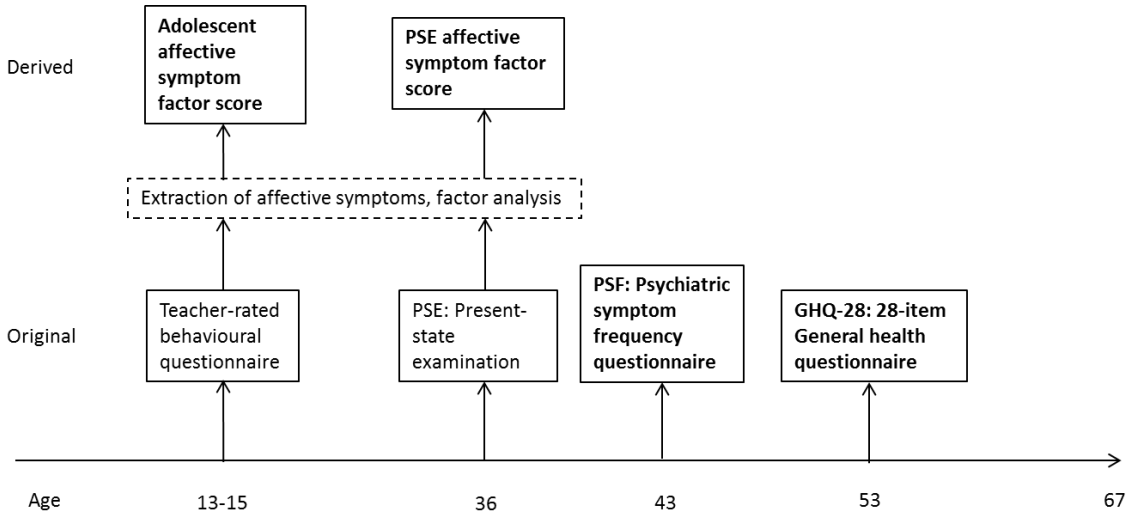

Figure 3.4.4 Original and derived affective symptom exposures at ages 13-15, 36, 43 and 53 years (bolded items represent measures used in analyses)

3.4.5 Age 36 and 43: Anxiety and depressive symptom scores

At age 36 and 43, items relating predominately to anxiety or depression were identified from the twenty-item PSE (see section 3.4.2.1 for detail) and PSF questionnaires, based on the Diagnostic and Statistical Manuals III-IV and ICD-9 definitions (American Psychiatric Association, 1994, 1980; World Health Organization, 1998). It was not appropriate to use the GHQ-28 at age 53 to compare depression and anxiety as the items relating to depression were far more severe than those relating to anxiety (see Appendix D for list of items). Likewise, the measure of affective symptoms at ages 13-15 pre-dated modern definitions of anxiety and depression, so these constructs were often conflated or vague and therefore difficult to specify; for example, 'Tends to become unduly miserable or worried'; 'A timid child'.

The twenty-item PSE and PSF questionnaires were subjected to exploratory factor analysis using a one, two, and three-factor solution. Items that potentially represented either anxiety or depression, such as 'easily tired', were classified depending on their loading in relation to less-ambiguous items, such as 'depressed mood'; (see Appendices B and C for detail of item classification).

Factor analyses on the PSF at age 43 also revealed that two-items loaded strongly on a separate factor relating to sleep disturbance: 'Have you had trouble getting off to sleep?' and 'Have you had trouble with waking up and not being able to get back to sleep?'; a separate score was used to examine these items independently. A separate factor relating to sleep disturbance has also been identified in a previous study using the GHQ-28 (Molina et al., 2006).

The anxiety, depressive, and sleep disturbance scores were summed and then standardised prior to analysis.

Separate analyses were not conducted on items such as fatigue/tiredness or somatic-affective symptoms as factor analyses of the PSE and PSF questionnaires provided no evidence that these items represented a distinct construct.

3.4.6 Cut-offs for affective symptom measures at age 13/15, 36, 43 and 53

Categorical variable – none/mild, moderate, and severe symptoms:

For each of the affective symptom measures at ages 13-15, 36, and 43 years, those scoring in the top 16% were classified as having 'severe' symptoms, based on the estimated prevalence of CMD in the UK population (McManus et al., 2009). Study members within the 50th percentile were classified as having 'no/mild' symptoms, which is consistent with other studies (Colman et al., 2007a; Henderson et al., 2011), and all other study members between the 50th and 84th percentile were classified as experiencing 'moderate' symptoms.

At age 53, severe affective symptoms were defined by using the established and validated GHQ Likert scoring (0-1-2-3) cut point of 23/24 (Goldberg et al., 1997; Goldberg and Hillier, 1979; Lobo et al., 1986) as sensitivity analysis showed that the association between affective symptoms and mortality was unaffected if using a cut-point of 16%, or the standard GHQ Likert scoring cut-point. The proportion of those classified as having 'severe' affective symptoms using the above cut-off was 18.4% (Table 3.5.5); study members within the 50th percentile were classified as having 'no/mild' symptoms, and all others were classed as experiencing 'moderate' symptoms.

Binary variable – 'caseness':

'Caseness' refers to a level of symptom severity consistent with a possible clinical diagnosis of affective disorder.

At ages 13-15, 36, and 43, all those scoring in the top 16% were defined as an affective 'case' and all others with moderate and no/mild symptoms as a non-case. At age 53, an affective case was defined using the GHQ-scoring method (0-0-1-1) cut point of 5/6, which happened to identify 16.4% as an affective case – consistent with ages 13-15, 36, and 43 (summarised in table 3.4.6). The traditional cut-point for the GHQ-scoring method is 4/5 (Goldberg and Hillier, 1979); however more recent studies have shown that a cut-point of 5/6 offers improved levels of sensitivity and specificity (Goldberg et al., 1997; Lobo et al., 1986).

Table 3.4.6 Affective symptom measure cut-points for categorical and binary variables

		Categorical			Binary
Age	**Measure**	**None/mild**	**Moderate**	**Severe**	**'Case'**
13-15	Adolescent affective symptom factor score	<50th percentile	50th-84th percentile	Top 16 %	Top 16 %
36	Present-state-examination (PSE) affective symptom factor score	<50th percentile	50th-84th percentile	Top 16 %	Top 16 %
43	Psychiatric Symptom Frequency questionnaire (PSF)	<50th percentile	50th-84th percentile	Top 16 %	Top 16 %
53	General Health Questionnaire (GHQ-28)	<50th percentile	50th-82nd percentile	GHQ case, Likert score 23/24 (top 18%)	GHQ case, Method score 5/6 (top 16%)

3.4.7 Affective case accumulation, ages 13-15, 36, 43 and 53

A variable representing lifetime accumulation of severe affective symptoms was derived by adding the total number of times study members were classified as an affective case across ages 13-15, 36, 43, and 53. Those who were a case 3 or 4 times were combined into a single group since less than 1% of study members reported severe symptoms at all four time-points.

3.4.8 Affective case history, ages 13-15, 36, 43 and 53

An affective case history variable was created to explore the timing and duration of affective symptom onset. Five profiles were created: 'never' represented study members who were never an affective case; 'adolescent only' were those who were a case at age 13-15 only; 'new' represented those who were a case at age 53 only; 'chronic' were those who were a case 3-4 times; and 'intermittent' represented all others who were a case 1-2 times. The 'never' and 'chronic' profiles were identical to the affective case accumulation categories '0' and '3-4', respectively (see Appendix E for cross-tabulation). For a more detailed breakdown of the timing of affective caseness, see table 5.3.6.2.

Colman et al., (2010) previously conducted latent variable analyses on the NSHD data and identified six distinct affective symptom profiles (as described in section 1.2.3). However,

these profiles were not used because the 'adult-onset' categories included all those whose symptoms originated from age 36 onwards and were therefore insensitive to 'new' affective symptoms, that is, those first occurring immediately prior to follow-up for mortality at age 53.

3.4.9 Comparability of affective symptom measures across ages 13/15, 36, 43, and 53

The lifetime affective symptom variable was constructed from four different measures of affective symptoms; the measures assessed symptoms over inconsistent time periods, had varying response categories, and also relied on different modes of data collection, including teacher-rated behaviour, self-report questionnaire, and nurse interview. Whilst no measure is directly comparable, it was judged to be acceptable to combine these measures to create a longitudinal variable, for the following reasons:

First, all adulthood measures at ages 36, 43, and 53 contain very similar items, commonly recognised as symptoms of anxiety or depression.

Second, validation studies have shown that among a community sample of young adults, the GHQ-28 was highly correlated with the PSE Index of Definition, and PSE total scores; particularly if using a cut-point of 5/6 (Banks, 1983).

Third, studies using the NSHD have shown that teacher-rated internalising problems at ages 13 and 15 were strongly associated with adult psychiatric outcomes at ages 36, 43, and 53 (Colman et al., 2007b). Furthermore, the PSE Index of definition, PSF and GHQ-28 scores have all shown similar patterns of association with psychotropic medication use (Colman et al., 2006).

Finally, factor analysis has shown that all four measures demonstrate a single factor solution (Goldberg and Hillier, 1979; Lindelow et al., 1997; Xu et al., 2013), which further implies they share the same underlying construct. Previous studies have attempted to improve longitudinal comparability by using Confirmatory Factor Analysis to generate factor scores for each of the affective symptom measures (Colman et al., 2007a). However, this approach was not employed because, as noted above, sensitivity analysis revealed that there was no difference in the association between affective symptoms and mortality whether using the total item-score or factor score for the PSE, and PSF questionnaire (results not shown). In addition, it was preferable to leave the GHQ-28 in its original form

as it is a widely used and validated indicator of affective disorder (Gibbons et al., 2004; Goldberg et al., 1997; Lobo et al., 1986).

3.5 Outcome: Mortality

Mortality data was obtained from the National Health Service Central Register from age 26 onwards; cause of death was coded according to the International Classification of Diseases (ICD) 9 and 10, and deaths from cardiovascular disease, cancer, externalising disorders (violent, accidental and suicidal deaths), and other causes were identified. Follow-up time was from ages 15, 36, 43, or 53 years (dependent on the timing of the exposure) to mortality, or censored due to emigration or end of October 2014.

3.6 Covariates

3.6.1 Socio-demographics

Social class, age 53:

Social class was defined according to the Registrar-General's classification and grouped into six classes: I, professional; II, managerial and technical; IIINM, skilled non-manual; IIIM, skilled manual; IV, partly-skilled manual; and V, unskilled manual. Social class at age 53 was based on the occupational social class of the head of the household.

Education, age 26:

Education was based-on the highest level of educational attainment or training equivalent attained by age 26 years, and grouped into four categories: no qualifications, vocational or 'O' (ordinary) level, 'A' (advanced) level and higher (degree or equivalent, or above).

3.6.2 Health status

All measures of health status were assessed by trained nurses in study members' homes or clinical research facility.

Systolic blood pressure, age 53:

Blood pressure was measured at age 53 using an automated digital oscillometric sphygmomanometer (Omron HEM-705; Omron Corp., Tokyo, Japan). Two consecutive blood pressure readings were taken during which the study member was seated and had rested for at least five minutes. The second reading was used for the analyses; however if the second reading was missing then the first was used instead (<1% of observations). Cohort members were also asked whether they had taken any antihypertensive medication in the last year; if so a correction value of 10mmHg was added to their reading (Cui et al., 2003). Previous research has shown that systolic blood pressure tracks over time (Ulmer et al., 2003; Wills et al., 2011), which implies that a single blood pressure reading can act as a good indicator of blood pressure trajectory.

Body-mass index, age 53:

Body mass index (BMI) at age 53 was calculated using standardised measurement of height and weight, and defined as weight/height^2. Previous research using the NSHD found that BMI trajectories track strongly through adulthood (Wills et al., 2010), which suggests that a single measure of BMI can act as a good indicator of lifetime BMI trajectory.

Lung function, age 53:

Lung function was measured by Forced expiratory volume in 1 second (FEV_1) using a Micro Medical Micro Plus spirometer. Two readings were taken and if the nurse rated an attempt as unsatisfactory then this were classed as missing data. The higher value of the two readings was taken, or if only one was available then this was used instead. Variation in FEV_1 across both trials was within 5% for 79.6% of the sample at 53 years (Richards et al., 2005).

Pulse rate, age 53:

Resting pulse rate at age 53 was taken by nurses after three minutes of rest, and determined as beats per minute (bpm) using the radial artery.

Self-reported health conditions, ages 43 and 53:

Self-reported health conditions were obtained at age 43 and 53 from nurse interviews at the study member's home. At age 43, study members were asked whether they had 'ever' had bronchitis, high blood pressure, heart trouble, cancer, stroke, or diabetes. At age 53,

study members were asked whether 'in the last ten years' (since the last study wave) they had experienced blood pressure problems, heart trouble, cancer, stroke, or diabetes, and whether in the last three years they had any chest illness, including bronchitis, that had kept them off work a week or more. A measure of lifetime health conditions was created by summing the total number of health conditions at ages 43 and 53, which were then grouped into four categories: 0, 1, 2 and 3+.

3.6.3 Health behaviours

Smoking status, ages 20, 25, 31, 36, 43, and 53:

Smoking data was collected by postal questionnaire up to age 31, whilst data for later years was obtained from nurse interviews at the study member's home. Current cigarette smoking status ('yes' or 'no') was available at ages 20, 25, 31, 36, 43, and 53 years. Study members who provided data for at least three waves and whose missing data was not sequential were classified into one of four smoking trajectories: 'Never smoker', a non-smoker at all available data collections; 'Predominantly non-smoker', a non-smoker for at least three data collections; 'Predominantly smoker', a smoker at four or more of the data collections; and 'Lifelong smoker', a smoker at all available data collections (Clennell et al., 2008). These trajectories were previously been shown to be a strong predictor of decline in lung function and all-cause mortality in the NSHD (Clennell et al., 2008).

Physical activity, ages 36, 43 and 53:

Self-reported physical activity levels were obtained at age 36, 43 and 53 years from nurse interviews at the study members' home.

At age 36 years, study members were asked how often they participated in 27 different leisure-time activities in the preceding month; activities were based on the Minnesota leisure-time physical activity questionnaire (Taylor et al., 1978). At age 43, study members reported the frequency of participation in any sports, vigorous leisure activities, or exercises per month, and at age 53, the frequency of participation in any sports, vigorous leisure activities or exercises, not including getting to and from work, in the last 4 weeks.

At each age, those who were inactive (no activity) were given a score of 0, those who were moderately active (1-4 activities) a score of 1, and those who were most active (5+ activities) a score of 2. Scores were summed across ages 36, 43, and 53 years to provide a

lifetime measure of physical activity. Study members were classified as inactive (scoring 0), moderately active (scoring 1 to 3), and most active (scoring 4 to 6).

Problem drinking, ages 43 and 53:

At ages 43 and 53 study members self-completed the CAGE questionnaire (Ewing, 1984), which is a validated screening tool used to detect alcohol abuse (Bush et al., 1987; Ewing, 1984; Mayfield et al., 1974). The questionnaire consists of four yes/no statements with reference to the last year: 'Have you ever felt you ought to Cut down your drinking?', 'Have people ever annoyed you by criticising your drinking?', 'Have you ever felt bad or guilty about your drinking?', and 'Have you ever had to have a drink first thing in the morning to steady your nerves or get rid of hangover'?. A score of two or more 'yes' answers was used to indicate potential alcohol abuse (Bush et al., 1987; Ewing, 1984). A variable representing problem drinking was defined by study members who scored two or more at ages 43 or 53.

Diet score (Eating Choices Index), ages 36, 43 and 53:

At ages 36, 43, and 53, study members were asked to complete a five-day diet diary whereby they were asked to record all food and drink consumed. This information was used to calculate a dietary score using the Eating Choices Index (ECI) (Pot et al., 2014; Richards et al., 2010). ECI scores are based on breakfast consumption, fruit portions, type of milk, and type of bread consumed. The index ranges from 4-20, with a score of twenty representing the healthiest diet. At each age, mean ECI scores were calculated across the five-day period for those who completed the diary on at least two days. A lifetime dietary score was created by finding the aggregate ECI score across ages 36, 43, and 53.

3.6.4 Psychotropic mediation

Antidepressant and anxiolytic use, ages 31, 36, 43 and 53:

Prescription medication use was collected by postal questionnaire at age 31 years, and by nurse interview at ages 36, 43, and 53 years. Medications were matched to a British National Formulary (BNF) code (British Medical Association & Pharmaceutical Society of Great Britain, 2002) by trained nurses. Anxiolytic and antidepressant use was defined by whether a survey member had at any age reported taking anxiolytic (BNF section 4.1.2) or antidepressant (BNF section 4.3) medication, respectively. Previous research using the

NSHD study has shown that prior use of antidepressant or anxiolytic medication was a very strong predictor of future use (Colman et al., 2006).

3.6.5 Social networks and stressful life events

Marital status, age 53:

Current marital status at age 53 was obtained from self-report questionnaire and used as a social network measure. Study members were categorised into single, married or cohabiting, and divorced or widowed.

Support from friends, age 43 and 53:

At ages 43 and age 53 study members were asked "Do you think that you have friends or neighbours or relatives who would help if a problem or crisis came up?" (always, often, sometimes, never), which was used to indicate instrumental support.

The large majority of study members (> 88%) reported 'always' having support. A lifetime measure of social support was derived whereby those who reported 'always' at ages 43 and 53 were classified as 'always' having support, whilst all other study members were categorised as 'often, sometimes, or never'.

Stressful life events, ages 36, 43, and 53:

Stressful life events (SLE) were assessed at ages 36, 43, and 53 by nurse interview at the study member's home. At age 36, information was collected on eight SLE, whilst at ages 43 and 53 information was obtained on sixteen SLE. At all ages, study members were asked to recall their experiences over the last twelve months. Events included death of a loved one, illness, injury, moving house, burglary, divorce or separation, and crises with regard to employment, family, and children (for a full description see Hatch et al., 2009). A lifetime measure of SLE was created by summing the total number of events experienced at ages 36, 43, and 53 years, which were then grouped into three categories: 0–5, 6–9, and 10+.

3.6.6 Adverse childhood experiences

Adverse Childhood Experience variables were initially selected *a priori* based on existing research (Richards et al., 1997; Rodgers, 1990; Rodgers et al., 1997) and if they were consistent with the definition of ACE used in this thesis (see section 1.5.8).

They included variables relating to parental divorce or separation, parental abuse or neglect, mother's management and understanding, parental death, and time spent in foster care or institutions. For consistency with figure 3.4.4, only adversities reported prior to the first measure of affective symptoms at age 13 were considered.

Exploratory analyses were used to establish which ACE was included in the multivariable models. Variables were excluded if they were weak predictors of both mortality and affective caseness, or if too few reported the adversity; for instance, only 19 study members who had been in foster care remained in the sample by age 53. A composite measure was not possible as there were too few individuals reporting two or more adversities prior to age thirteen.

Cleanliness of the child (neglect), age11:

Teachers were asked to rate the cleanliness of the study member at age 11 compared to other children in the class. A binary variable was created which was divided into 'Among the most clean/Average' and 'Among the least clean', which was used to indicate neglect.

Parental separation, up to age 13

A binary variable was created to indicate all study members whose parents had divorced or separated prior to age 13, and those who had not. Data were obtained by examining changes in parental marital status at each wave of the study up to then. If the reason for change was given as 'divorce' or 'separation', then study members were coded as having experienced parental separation.

Parental abuse, age 43

Parental abuse was assessed at age 43 by self-report questionnaire. Study members were asked whether 'as a child, do you feel you were mistreated by your parents in any way?' ('yes' or 'no'). Study members were also allowed open comment on the type of mistreatment, which indicated that of those who answered 'yes', approximately two-thirds

felt ‘restricted/unhappy’ whilst one-third felt ‘abused/neglected’ (Stewart-Brown et al., 2005); although the binary ‘yes/no’ variable was retained due to low numbers.

3.6.7 Other childhood factors

Childhood social class

Childhood social class was based on the social class of the study member’s father at age 11 years, or if this was unknown, at age 4 or 15 years, and coded according to the Registrar-General’s classification (see social class, age 53).

Childhood sickness absence (ages 6-12)

Childhood sickness absence was obtained from school records and reflected the total weeks absent from school due to illness from ages 6 to 12 years. Three categories were created: 0-4 weeks, 4-10 weeks, and 10+ weeks.

Adolescent Externalising

Externalising (conduct) problems were assessed by teachers using a forerunner to the Rutter B questionnaire (Rutter, 1967). At ages 13 and 15, teachers were asked to rate the study member’s behaviour compared to other children in the class. The questionnaires have been previously subjected to exploratory factor analysis using probit models for categorical outcomes in the statistical package Mplus 6.1, which identified an eleven-item factor consistent with externalising behaviour (Xu et al., 2013). Items loading on this factor were “frequently disobedient”, “difficult to discipline”, “restless”, “frequently cribs”, “lies to avoid trouble”, “unduly rough during play”, “a dare-devil”, “seeks attention”, “quarrelsome and aggressive”, “over-competitive”, and “resentful of criticism”. Factor scores were standardised at age 13 and 15, and then summed to create a single measure of adolescent externalising problems. Three categories were created based-on established percentile cut points from other studies (Colman et al., 2009; Richards and Abbott, 2009; Rodgers, 1990). These were ‘none’ (< 75%), ‘mild’ (75-93%), and ‘severe’ (93% and above).

3.6.8 Schizophrenia caseness

Schizophrenia caseness was ascertained in two stages. Firstly, evidence of potential schizophrenia was obtained using questionnaire and interview data on hospital contacts and GP visits from ages 16 to 43 years, the PSE at age 36, and central registry data on all admissions to psychiatric hospitals in England, Wales and Scotland. Secondly, DSM-IIIR (American Psychiatric Association, 1980) criteria were applied to the extracted material to identify schizophrenia or schizoaffective disorder caseness. For a more detailed description of how schizophrenia cases were ascertained, see Jones et al., (1994).

3.7 Analytical strategy and statistical methods used (shared)

This section describes an overview of statistical methods common across each of the analytical chapters, with further detail given in subsequent chapters.

Descriptive analyses were conducted by creating histograms and frequency tables to assess the distribution, means and range of each variable within the dataset. All variables were checked for potential outliers.

Crude associations between affective symptoms at ages 13-15, 36, 43, and 53, affective case accumulation and affective case history, with mortality, were examined using Kaplan-Meier graphs. Since time-to-event data was available for mortality, sex and multivariable adjusted associations were assessed using Cox regression. Multivariable adjusted models were used to investigate to what extent potential explanatory factors (e.g. chronic health conditions, health behaviours, and early-life factors) accounted for associations between affective case accumulation and affective case history, and mortality. The proportional hazards assumption was checked in all Cox models by including an interaction term between log-time and the main exposure, which was used to test whether associations were consistent over follow-up. Associations between affective case accumulation and affective case history, with cause-specific mortality were examined using competing-risks analyses, as cause of death is mutually exclusive. Competing-risks analysis takes into consideration deaths from other causes, which if unaccounted for, may result in misleading estimates.

To assess whether associations between affective symptoms or caseness, and mortality were different in men and women, sex interactions were tested using Likelihood ratio $\chi 2$

tests in non-imputed data, and joint Wald tests in imputed data. Sex interactions were not statistically significant in any model; however most analyses were presented by sex due to the substantially higher prevalence of affective symptoms and caseness reported by women.

For all models, power analyses using OpenEpi Version 3.0.1 (Dean et al., 2006) were conducted to determine the level of statistical power for detecting a range of possible effect sizes, and thus whether analyses were feasible.

Statistical analyses were conducted using Stata 13 (StataCorp LP, 2013), unless otherwise indicated.

4. AFFECTIVE SYMPTOMS AND MORTALTY OVER THE LIFE COURSE

4.1 Chapter overview

This chapter presents results of analyses relating to objective 1: To investigate the association between affective symptoms and mortality with respect to age, symptom severity, and symptom type. The following hypotheses were tested:

1. Affective symptoms are associated with mortality across the life course (ages 13-15, 36, 43, and 53)
2. Severe affective symptoms are more strongly associated with mortality compared to moderate or mild symptoms
3. Both anxiety and depressive symptoms are equally predictive of mortality

Descriptive analysis of affective symptoms and mortality are presented for ages 13-15, 36, 43, and 53 years. Crude and sex adjusted associations between affective symptoms and mortality are demonstrated at each age, accompanied by sensitivity analyses. Finally, the effects of different types of affective symptoms at ages 36 and 43 years are presented, followed by a discussion of the results.

4.2 Methods

4.2.1 Exposure variables

The main exposure variables used in this chapter are affective symptoms at ages 13-15, 36, 43 and 53 categorised into mild, moderate and severe symptoms (as previously described in section 3.4).

At ages 36 and 43, separate anxiety and depressive symptom scores were derived in order to examine the role of different types of affective symptoms. At age 43, two items relating to sleep disturbance were found to load strongly onto a separate factor therefore an additional sleep disturbance score was created (see section 3.4.5 for further detail).

4.2.2 Outcome variable

The outcome variable was all-cause mortality (as described previously in section 3.5), with follow-up from ages 13-15, 36, 43, or 53 depending on the timing of the affective symptom measure.

4.2.3 Analytical strategy

Descriptive analyses were conducted on affective symptoms and mortality data at ages 13-15, 36, 43, and 53. At each age, Kaplan Meier graphs were produced to show the unadjusted association between affective symptoms and mortality over-time, and log-rank tests were used to test the equality of survival curves. Mortality follow-up interval was dependent on the timing of the affective symptom measure, ranging from age 13-15 to age 53.

Cox regression models were used to test the relationship between affective symptoms and mortality after adjustment for sex. Sensitivity analyses were conducted i) excluding schizophrenia cases to test whether this disorder explained associations with mortality; ii) excluding externalising deaths to test whether associations could be explained by violent or accidental deaths, or suicide; and iii) including a 3-year wash-out period to test for reverse causality, that is, whether affective symptoms occur as a psychological consequence of serious illness, and/or as a result of inflammation due to sub-clinical 'unknown' illness such as atherosclerosis or cancer.

Power calculations were conducted for each time-point. Sex interactions were tested using Likelihood ratio $\chi 2$ tests. The proportional hazards assumption was assessed by including an interaction term between log-time and affective symptoms, and sex. Across all analyses, there was no evidence that the proportional hazards assumption was violated with respect to either moderate or severe affective symptoms.

The relative influence of anxiety, depressive, and sleep disturbance scores on mortality were examined using Cox Regression. All models were adjusted for sex and then in order to estimate the independent role of anxiety and depression, anxiety scores were further adjusted for depression, and vice versa. Pearson's correlation coefficients were calculated for the association between anxiety and depressive scores to ensure mutual adjustment was feasible.

4.2.4 Participants

At each age, participants included in analyses were all study members who had linked mortality data with the National Health Service Central Register, and had complete data on affective symptoms (see figure 4.2.4).

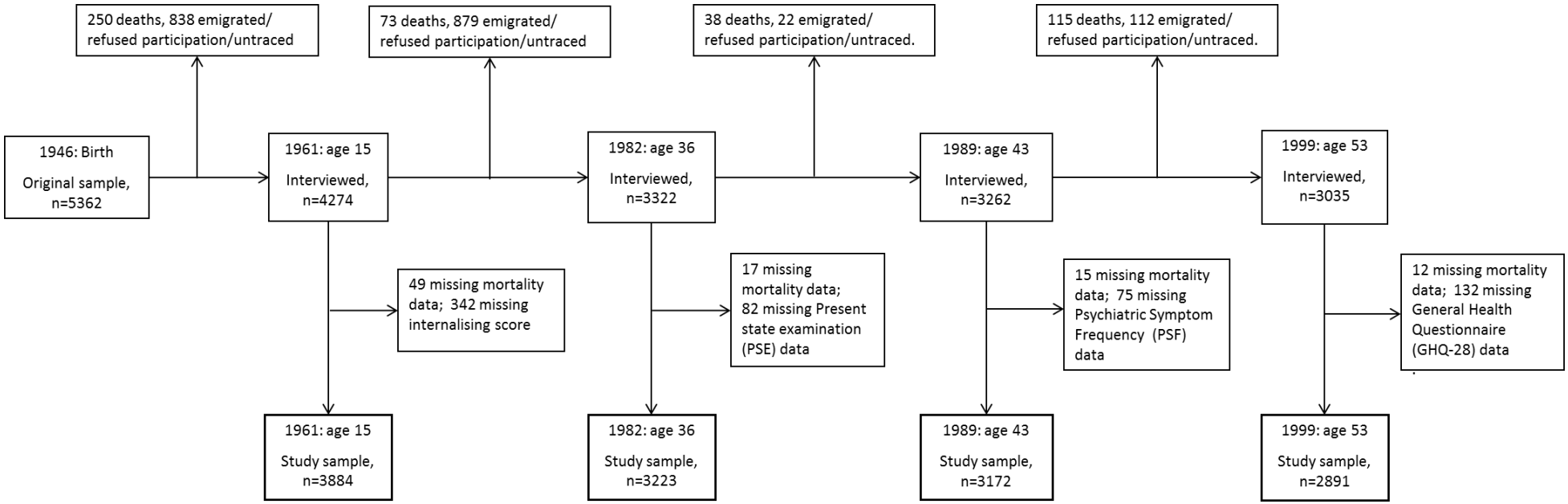

Fig 4.2.4 Participant flow from original sample (n=5362) to study samples at ages 15, 36, 43, and 53 years

4.3 Results

4.3.1 Descriptive characteristics of affective symptoms at ages 13-15, 36, 43 and 53

Tables 4.3.1.1-4 show the proportion of study members classified as having no/mild, moderate, or severe affective symptoms at ages 13/15, 36, 43 and 53 years. Consistent with numerous studies, females were considerably more likely to report severe symptoms at all ages. At age 53, the proportion of study members classified as severe was slightly higher compared to other ages, which reflects the use of the standard GHQ-28 Likert-scoring cut point, which is the recommended scoring method for assessing symptom severity (as previously discussed in section 3.4.6).

Table 4.3.1.1 Descriptive characteristics of affective symptoms at age 13-15 by sex

	All (n=3884)		**Males** (n=2016)	**Females** (n=1868)
	n	%	%	%
Affective symptoms				
None/mild	2,001	51.52	55.46	47.27
Moderate	1,253	32.26	30.75	33.89
Severe	630	16.22	13.79	18.84

Table 4.3.1.2 Descriptive characteristics of affective symptoms at age 36 by sex

	All (n=3223)		**Males** (n=1610)	**Females** (n=1613)
	n	%	%	%
Affective symptoms				
None/mild	1,712	53.12	58.70	47.55
Moderate	993	30.81	29.81	31.80
Severe	518	16.07	11.49	20.64

Table 4.3.1.3 Descriptive characteristics of affective symptoms at age 43 by sex

	All (n=3172)		**Males** (n=1593)	**Females** (n=1579)
	n	%	%	%
Affective symptoms				
None/mild	1,615	50.91	56.94	44.84
Moderate	1,042	32.85	30.45	35.28
Severe	515	16.24	12.62	19.89

Table 4.3.1.4 Descriptive characteristics of affective symptoms at age 53 by sex (GHQ-28 Likert scoring)

	All (n=2891)		**Males** (n=1419)	**Females** (n=1472)
	n	%	%	%
Affective symptoms				
None/mild	1,542	53.34	61.24	45.72
Moderate	810	28.02	25.93	30.03
Severe	539	18.64	12.83	24.25

4.3.1.5 Attrition by affective symptom severity

Table 4.3.1.5 shows that there was evidence of greater attrition among those with severe and moderate affective symptoms compared to those with no/mild symptoms. Those with severe symptoms demonstrated the greatest loss to follow-up, followed by those with moderate symptoms. The effect was most pronounced at age 13-15 whereby participation was almost 10% lower among those with severe symptoms, compared to those with no/mild symptoms.

Table 4.3.1.5 Percentage of study members participating at age 53

		Participation at age 53 (%)
Age 13-15	None/mild	67.0
	Moderate	63.0
	Severe	58.7
Age 36	None/mild	83.1
	Moderate	82.5
	Severe	81.7
Age 43	None/mild	88.2
	Moderate	87.1
	Severe	83.7

4.3.2 Descriptive characteristics of mortality at ages 13-15, 36, 43 and 53

Figure and table 4.3.2.1 show mortality descriptives by age of follow-up.

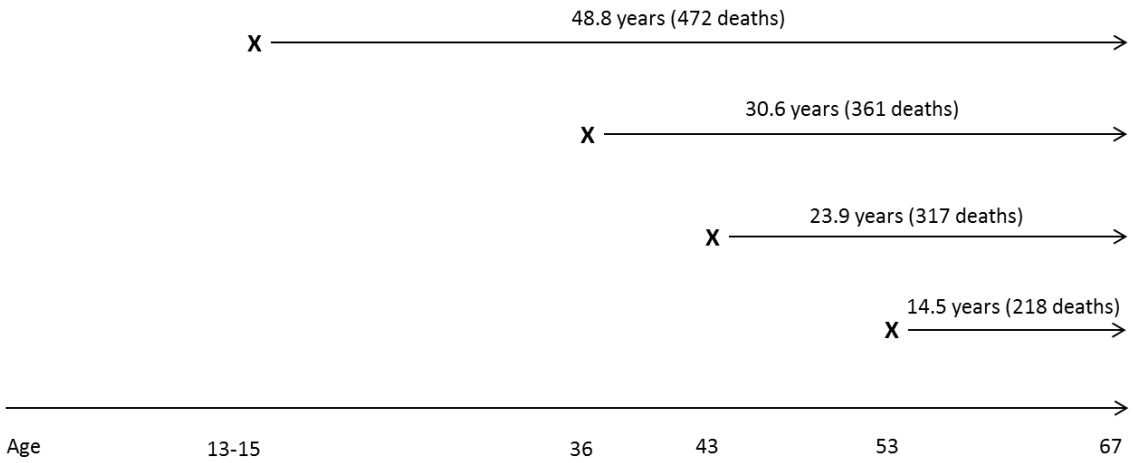

Figure 4.3.2.1 Mean follow-up time and number of deaths by affective symptom exposures at ages 13-15, 36, 43 and 53 years

Table 4.3.2.1 Total death, follow-up time, and incidence by age of follow-up

	Deaths (n)	Years of follow-up, mean (range)	Total follow-up time (person-years)	Incidence (per 10,000 person years)
Follow-up				
Age 15	472	48.8 (3.4-53)	189,609	24.89
Age 36	361	30.6 (1.6-32)	98,671	36.59
Age 43	317	23.9 (0.9-25)	75,949	41.74
Age 53	218	14.5 (0.7-15)	41,937	51.98

Figure 4.3.2.2 and table 4.3.2.2 show that across all ages of follow-up, the most common cause of death is cancer, followed by cardiovascular disease. The proportion of cancer deaths at age 53 is slightly larger compared to earlier ages of follow-up, and the proportion of externalising deaths appears to markedly decrease as age of follow-up increases. The proportion of those dying from cardiovascular and 'other' causes appears relatively stable over time.

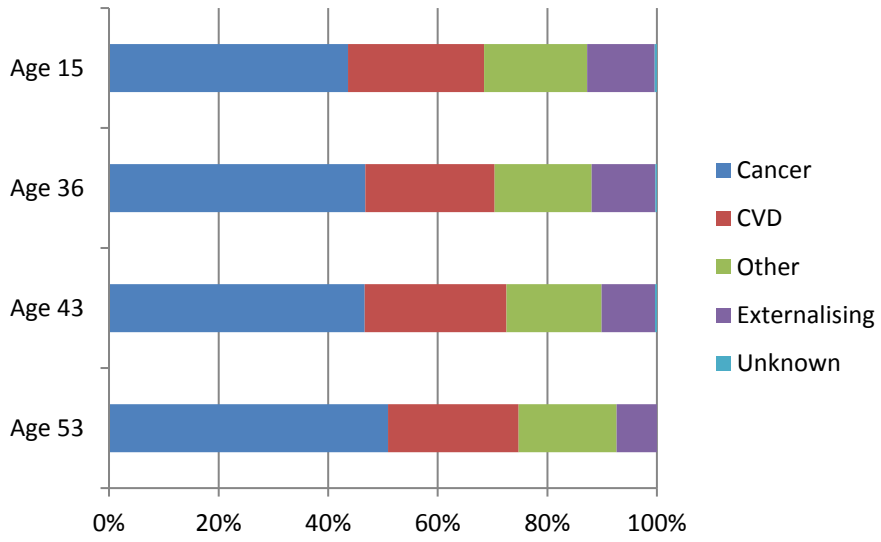

Figure 4.3.2.2 Cause of death by age of follow-up for mortality

Table 4.3.2.2 Cause of death by age of follow-up for mortality

Cause of death	Age 15		Age 36		Age 43		Age 53	
	n	%	n	%	n	%	n	%
Cancer	206	43.64	169	46.81	148	46.69	111	50.92
CVD	117	24.79	85	23.55	82	25.87	52	23.85
Other	89	18.86	64	17.73	55	17.35	39	17.89
Externalising	58	12.29	42	11.63	31	9.78	16	7.34
Unknown	2	0.42	1	0.28	1	0.32	0	0
Total	472	100	361	100	317	100	218	100

4.3.3 Crude and sex adjusted associations between mortality and affective symptoms at ages 13-15, 36, 43 and 53

4.3.3.1 Power analyses for the association between mortality and affective symptoms at ages 13-15, 36, 43, and 53

Statistical power refers to the probability of not making a type II error (falsely concluding that there is no difference between exposure groups when there is one). A power level of 80% is usually considered 'good' as this means a statistical test will be likely to detect an effect eight times out of ten. Power is primarily a function of sample size and effect size; for instance, a large sample would be needed to provide sufficient power to detect a small effect. Tables 4.3.3.1-4 show that as follow-up age increases, power decreases, largely due to sample attrition. Tables 4.3.3.1.1 and 4.3.3.1.2 show that at age 13-15 and 36 years, there is good power to detect hazard ratios in the region of 1.3 or larger for moderate symptoms, and 1.4 or larger for severe symptoms. Tables 4.3.3.1.3 shows that at age 43, there is sufficient power to detect hazard ratios of 1.4 or larger for moderate symptoms and 1.5 or larger for severe symptoms, whilst table 4.3.3.1.4 shows that at age 53 there is good power to detect hazard ratios of 1.5 or larger for moderate symptoms, and 1.6 or larger for severe symptoms. At all ages there appears to be a high chance of type II error for hazard ratios under 1.2, which means that small effects may not have been detected.

Table 4.3.3.1.1 Power at age 13/15 for moderate and severe affective symptoms based on 10.8% risk of all-cause mortality among those with no affective symptoms (n=2001), alpha 0.05

	Power (%)	
	Moderate symptoms (n=1253)	**Severe symptoms (n=630)**
Hazard ratio		
1.2	46.4	32.0
1.3	78.9	60.2
1.4	95.3	83.1
1.5	99.4	95.3
1.6	100.0	99.1
1.8	100.0	99.9
2.0	100.0	100.0

Table 4.3.3.1.2 Power at age 36 for moderate and severe affective symptoms based on 10.9% risk of all-cause mortality among those with no affective symptoms (n=1712), alpha 0.05

	Power (%)	
	Moderate symptoms (n=993)	**Severe symptoms (n=518)**
Hazard ratio		
1.2	34.6	25.9
1.3	71.0	52.8
1.4	90.4	75.5
1.5	98.3	91.4
1.6	99.7	97.3
1.8	100.0	99.9
2.0	100.0	100.0

Table 4.3.3.1.3 Power at age 43 for moderate and severe affective symptoms based on 9.0% risk of all-cause mortality among those with no affective symptoms (n=1615), alpha 0.05

	Power (%)	
	Moderate symptoms (n=1042)	**Severe symptoms (n=515)**
Hazard ratio		
1.2	33.4	22.9
1.3	61.8	43.9
1.4	84.3	66.5
1.5	95.5	84.0
1.6	99.1	94.0
1.8	99.9	99.6
2.0	100.0	99.9

Table 4.3.3.1.4 Power at age 53 for moderate and severe affective symptoms based on 6.7% risk of all-cause mortality among those with no affective symptoms (n=1542), alpha 0.05

	Power (%)	
	Moderate symptoms (n=810)	**Severe symptoms (n=539)**
Hazard ratio		
1.2	22.7	18.4
1.3	42.6	34.3
1.4	64.8	53.9
1.5	81.9	71.7
1.6	92.7	85.4
1.8	99.4	97.7
2.0	100.0	99.8

4.3.3.2 Crude and sex adjusted associations between affective symptoms at age 13-15 and mortality

Figure 4.3.3.2 shows that study members who experienced severe affective symptoms at age 13/15 had the lowest survival probability, followed by those with moderate and those with no/mild symptoms. The survival curves begin, and continue to diverge at approximately thirty-five years of follow-up (age 50), particularly for those with severe symptoms. The Log-rank test showed that there was a difference in survival curves, $\chi^2(2)= 11.39$, $p=0.003$.

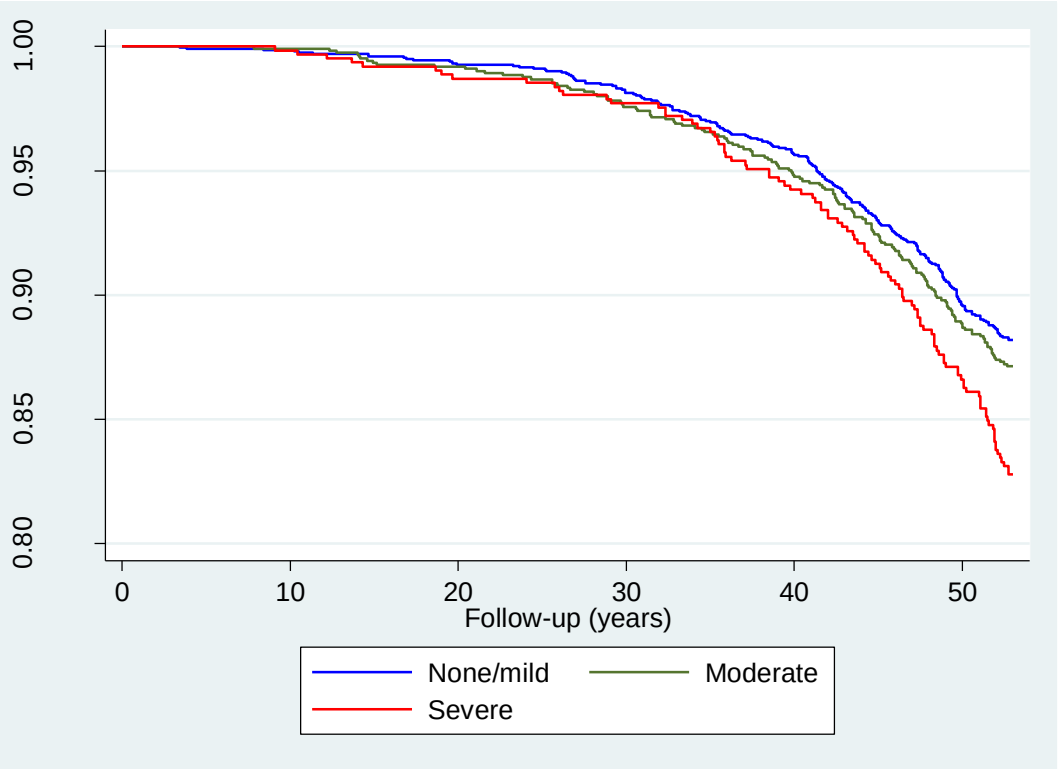

Figure 4.3.3.2 Unadjusted Kaplan-Meier survival curves for all-cause mortality by affective symptoms at age 13-15; 343 deaths, n=3884

Table 4.3.3.2.1 shows that after adjustment for sex, severe affective symptoms at age 13/15 were associated with an increased risk of mortality compared to no/mild symptoms. The hazard ratio for moderate symptoms was slightly raised, although the association is not statistically significant.

Women showed a stronger association between severe symptoms and mortality compared to men; however there was no evidence of a sex interaction (likelihood-ratio test $\chi^2(2) = 0.84$, p=0.66).

Table 4.3.3.2.1 Sex adjusted hazard ratios for the association between affective symptoms at age 13/15 and mortality

	Hazard ratio (95% CI)		
	Sex adjusted (n=3884, 472 deaths)	**Males** (n=2016, 268 deaths)	**Females** (n=1868, 204 deaths)
Affective symptoms			
None/mild	ref	ref	ref
Moderate	1.12 (0.91, 1.38)	1.12 (0.85, 1.47)	1.12 (0.81, 1.55)
Severe	1.54 (1.22, 1.94)**	1.39 (1.00, 1.93)	1.71 (1.22, 2.40)*

* $p < 0.05$
** $p < 0.005$

Table 4.3.3.2.2 shows that after adjustment for sex, the hazard ratio for severe symptoms was slightly raised after excluding externalising deaths. In contrast, the hazard ratios were unaffected by excluding schizophrenia cases, and the inclusion of a three year wash-out period.

Table 4.3.3.2.2 Sex adjusted hazard ratios for the association between affective symptoms at age 13/15 and mortality, excluding schizophrenia cases, excluding externalising deaths, and including a 3-year wash-out

	Hazard ratio (95% CI)			
	Sex adjusted (n=3884, 472 deaths)	**+ excluding schizophrenia** (n=3855, 462 deaths)	**+ excluding externalising deaths** (n=3826, 414 deaths)	**+ 3-year wash-out** (n=3608, n=433 deaths)
Affective symptoms				
None/mild	ref	ref	ref	ref
Moderate	1.12 (0.91, 1.38)	1.12 (0.90, 1.38)	1.07 (0.85, 1.34)	1.09 (0.87, 1.35)
Severe	1.54 (1.22, 1.94)**	1.52 (1.20, 1.93)*	1.67 (1.31, 2.13)**	1.54 (1.20, 1.96)**

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

4.3.3.3 Crude and sex adjusted associations between affective symptoms at age 36 and mortality

Figure 4.3.3.3 shows that study members who experienced severe affective symptoms at age 36 had a slightly lower survival probability compared to those with no/mild and moderate symptoms, and that this difference becomes most apparent in later years of follow-up. There was no overall difference in survival curves, Log Rank $\chi^2(2)= 1.56$, p=0.46.

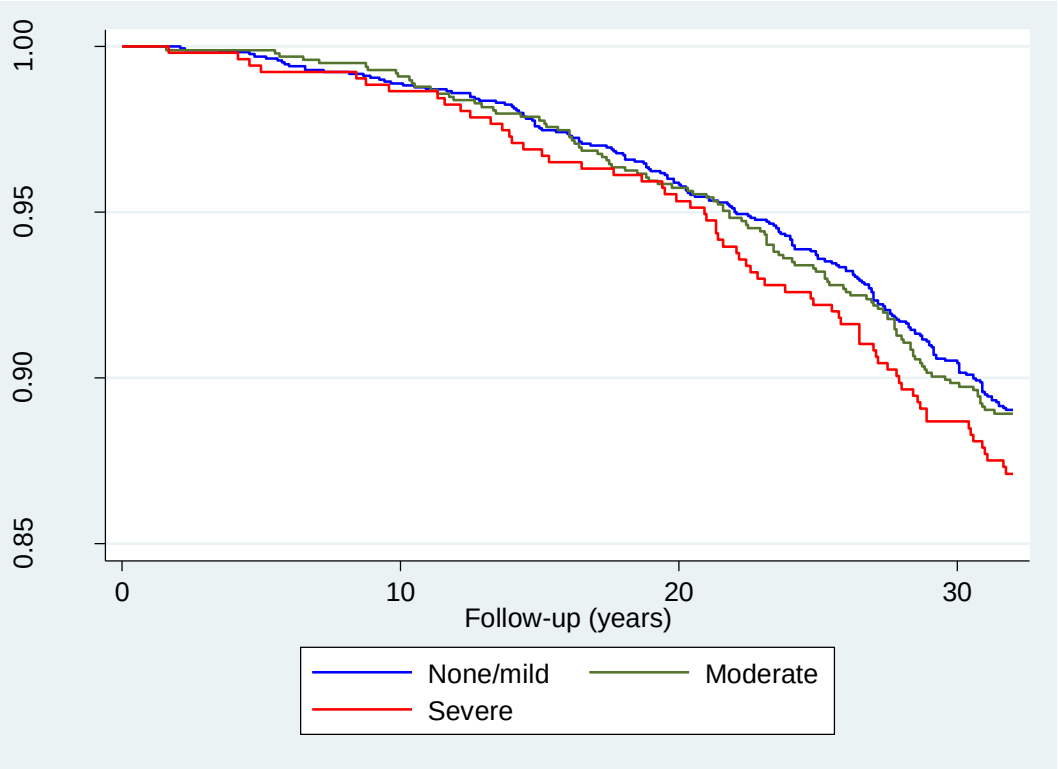

Figure 4.3.3.3. Unadjusted Kaplan-Meier survival curves for all-cause mortality by affective symptoms at age 36; 361 deaths, n=3223.

Table 4.3.3.3.1 shows that after adjustment for sex, moderate and severe affective symptoms at age 36 were not associated with mortality. Across all models, the hazard ratio for severe symptoms were slightly raised, although the associations were not statistically significant. There was no evidence of a sex-interaction (likelihood-ratio test $\chi^2(2)= 0.99$, p=0.61).

Table 4.3.3.3.1 Hazard ratios for the association between affective symptoms at age 36 and mortality, by sex

	Hazard ratio (95% CI)		
	Sex adjusted (n=3223, 361 deaths)	**Males** (n=1610, 200 deaths)	**Females** (n=1613, 161 deaths)
Affective symptoms			
None/mild	ref	ref	ref
Moderate	1.03 (0.81, 1.31)	1.11 (0.82, 1.52)	0.93 (0.64, 1.35)
Severe	1.25 (0.94, 1.66)	1.16 (0.75, 1.78)	1.30 (0.89, 1.91)

Table 4.3.3.3.2 shows that after adjustment for sex, the hazard ratio for severe symptoms was unaffected after excluding schizophrenia cases and externalising deaths, and including a three year wash-out period. However, the hazard ratio for moderate symptoms appeared marginally raised after the exclusion of externalising deaths.

Table 4.3.3.3.2 Sex adjusted hazard ratios for the association between affective symptoms at age 36 and mortality, excluding schizophrenia cases, excluding externalising deaths, and including a 3-year wash-out

	Hazard ratio (95% CI)			
	Sex adjusted (n=3223, 361 deaths)	**+ excluding schizophrenia** (n=3199, 335 deaths)	**+ excluding externalising deaths** (n=3181, 319 deaths)	**+ 3-year wash-out** (n=3219, 357 deaths)
Affective symptoms				
None/mild	ref	ref	ref	ref
Moderate	1.03 (0.81, 1.31)	1.01 (0.79, 1.28)	1.15 (0.90, 1.47)	1.03 (0.81, 1.31)
Severe	1.25 (0.94, 1.66)	1.21 (0.91, 1.62)	1.27 (0.93, 1.72)	1.24 (0.93, 1.66)

4.3.3.4 Crude and sex adjusted associations between affective symptoms at age 43 and mortality

Figure 4.3.3.4 shows that study members who experienced severe affective symptoms at age 43 had a lower survival probability compared to those with moderate and no/mild symptoms. There was little difference in the survival probability of those with moderate and no/mild symptoms by the end of follow-up; however the Log Rank test showed an overall difference in survival curves, $\chi^2(2)= 19.7$, $p <0.001$.

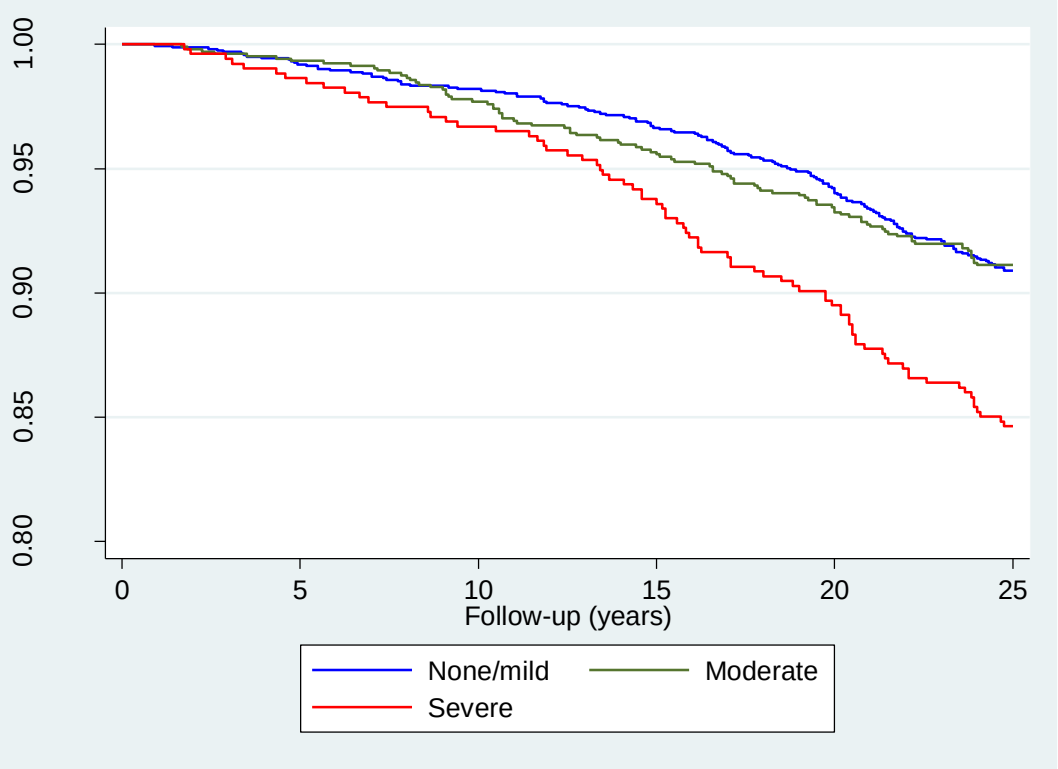

Figure 4.3.3.4 Unadjusted Kaplan-Meier survival curves for all-cause mortality by affective symptoms at age 43; 317 deaths, n=3172.

Table 4.3.3.4.1 shows that after adjustment for sex, severe affective symptoms at age 43 were associated with a considerably increased risk of mortality compared to no/mild symptoms; however there was no association between moderate symptoms and mortality.There was no evidence of a sex interaction (likelihood-ratio test $\chi^2(2) = 0.48$, $p=0.48$).

Table 4.3.3.4.1 Hazard ratios for the association between affective symptoms at age 43 and mortality, by sex

	Hazard ratio (95%CI)		
	Sex adjusted (n=3172, 317 deaths)	**Males** (n=1593, 180 deaths)	**Females** (n=1579, 137 deaths)
Affective symptoms			
None/mild	ref	ref	ref
Moderate	1.02 (0.78, 1.32)	1.03 (0.74, 1.47)	0.97 (0.65, 1.46)
Severe	1.86 (1.41, 2.46)**	2.04 (1.40, 2.96) **	1.68 (1.11, 2.52)*

** p < 0.001

Table 4.3.3.4.2 shows that after adjustment for sex, the hazard ratio for moderate symptoms was unaffected after excluding schizophrenia cases and externalising deaths, and the inclusion of a three year wash-out period. However, the hazard ratio for severe symptoms was slightly attenuated after excluding externalising deaths.

Table 4.3.3.4.2 Sex adjusted hazard ratios for the association between affective symptoms at age 43 and mortality, excluding schizophrenia cases, excluding externalising deaths, and including a 3-year wash-out

	Hazard ratio (95% CI)			
	Sex adjusted (n=3172, 317 deaths)	**+ excluding schizophrenia** (n=3150, 311 deaths)	**+ excluding externalising deaths** (n=3141, 286 deaths)	**+3-year wash-out** (n=3160, 305 deaths)
Affective symptoms				
None/mild	ref	ref	ref	ref
Moderate	1.02 (0.78, 1.32)	1.01 (0.78, 1.32)	1.00 (0.76, 1.32)	1.00 (0.77, 1.31)
Severe	1.86 (1.41, 2.46)**	1.82 (1.37, 2.41)**	1.74 (1.30, 2.34)**	1.85 (1.40, 2.45)**

** p < 0.001

4.3.3.5 Crude and sex adjusted associations between affective symptoms at age 53 and mortality

Figure 4.3.3.5 shows that study members who experienced severe affective symptoms at age 53 had the lowest survival probability, followed by those with moderate and those with no/mild symptoms. The survival curves no longer diverged after approximately seven years of follow-up, suggesting that the role of affective symptoms weakened. There was no overall difference in survival curves, Log Rank $\chi^2(2)= 4.51$, p=0.11.

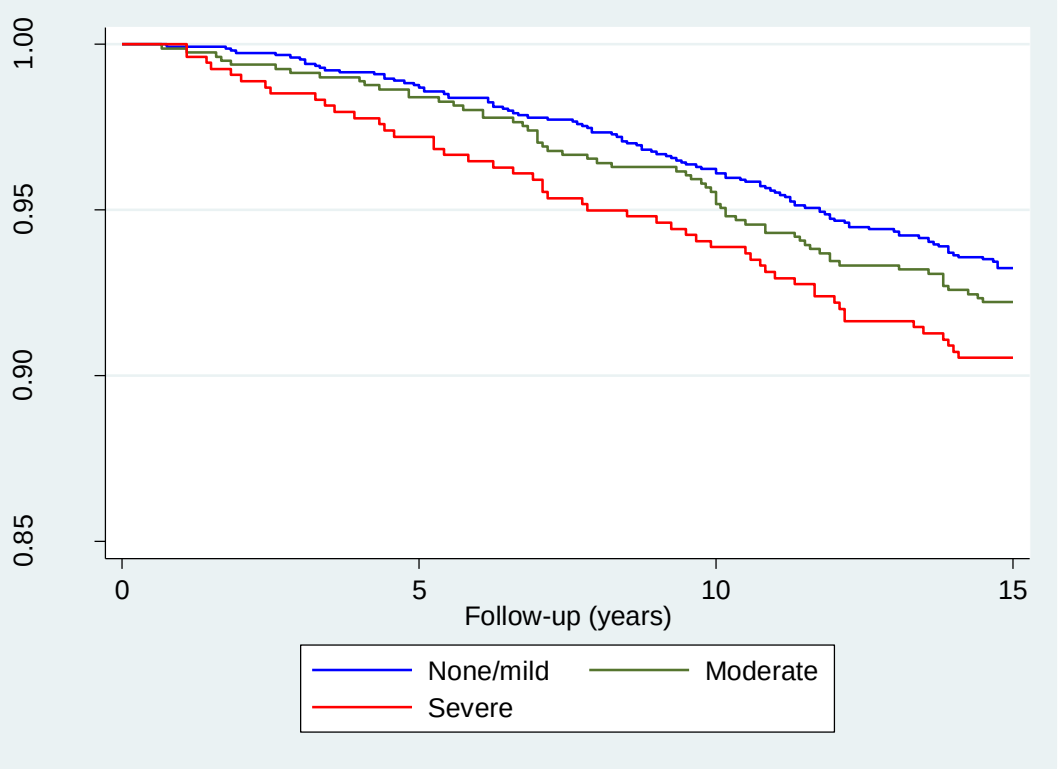

Figure 4.3.3.5 Unadjusted Kaplan-Meier survival curves for all-cause mortality by affective symptoms at age 53; 218 deaths, n=2891.

Table 4.3.3.5.1 shows that after adjustment for sex, severe affective symptoms at age 53 were associated with an increased risk of mortality compared to no/mild symptoms. The hazard ratio for moderate symptoms is also raised, suggestive of a dose-response relationship; however the association is not statistically significant.

There was no evidence of a sex interaction (likelihood-ratio test $\chi^2(2) = 0.88$, p=0.65).

Table 4.3.3.5.1 Hazard ratios for the association between affective symptoms at age 53 and mortality, by sex

	Hazard ratio (95% CI)		
	Sex adjusted (n=2891, 218 deaths)	**Males** (n=1419, 125 deaths)	**Females** (n=1472, 93 deaths)
Affective symptoms			
None/mild	ref	ref	ref
Moderate	1.21 (0.87, 1.66)	1.07 (0.70, 1.62)	1.45 (0.89, 2.37)
Severe	1.57 (1.11, 2.21)*	1.52 (0.94, 2.46)	1.70 (1.03, 2.80)*

* $p < 0.05$

Table 4.3.3.5.2 shows that after adjustment for sex, the hazard ratios were unaffected by the exclusion of schizophrenia cases. However, the hazard ratios for severe symptoms were slightly attenuated after excluding externalising deaths, and the inclusion of a three year wash-out period.

Table 4.3.3.5.2 Sex adjusted hazard ratios for the association between affective symptoms at age 53 and mortality, excluding schizophrenia cases, excluding externalising deaths, and including a 3-year wash-out

	Hazard ratio (95% CI)			
	Sex adjusted (n=2891, 218 deaths)	**+ excluding schizophrenia** (n=2877, 216 deaths)	**+ excluding externalising deaths** (n=2875, 202 deaths)	**+ 3-year wash-out** (n=2869, 196 deaths)
Affective symptoms				
None/mild	ref	ref	ref	ref
Moderate	1.21 (0.87, 1.66)	1.20 (0.87, 1.64)	1.18 (0.85, 1.63)	1.16 (0.83, 1.61)
Severe	1.57 (1.11, 2.21)*	1.55 (1.10, 2.18)*	1.49 (1.04, 2.12)*	1.43 (0.99, 2.06)

* $p < 0.05$

4.3.4 Sex adjusted associations between mortality and standardised anxiety, depressive and sleep disturbance symptoms at age 36 and 43

Table 4.3.4 compares the effect of anxiety, depressive, and sleep disturbance symptoms on mortality.

At both ages 36 and 43, the sex adjusted hazard ratios for standardised anxiety and depressive symptom scores are very similar. At age 43, the associations were partially attenuated after adjustment for respective anxiety and depressive symptoms; however the influence of anxiety and depressive symptoms on mortality remained comparable. At age 36, the hazard ratios indicate a similar trend.

The anxiety and depressive scales were positively correlated at ages 36 (r=0.60) and 43 (r=0.79); although there was no evidence of multi-collinearity when both scales were included in the model together.

At age 43, there was no association between the study member's standardised sleep disturbance score and mortality.

There was no evidence of a sex interaction across any analyses at ages 36 or 43.

Table 4.3.4 Sex adjusted associations between mortality and standardised anxiety, depressive and sleep disturbance symptoms at age 36 and 43

	Hazard ratio (95% CI)		
	Sex adjusted	**Sex + depressive symptoms**	**Sex + anxiety symptoms**
Age 36[a]			
Anxiety	1.09 (0.99, 1.21)	1.07 (0.94, 1.22)	-
Depression	1.07 (0.97, 1.18)	-	1.03 (0.91, 1.17)
Age 43[b]			
Anxiety	1.23 (1.11, 1.35)**	1.10 (0.93, 1.31)	-
Depression	1.23 (1.12, 1.34)**	-	1.13 (0.96, 1.33)
Sleep	1.07 (0.96, 1.18)	-	-

a: Based on 3000 study members and 342 deaths

b: Based on 3172 study members and 317 deaths

** $p < 0.001$

4.4 Discussion

The analytical models at ages 13/15, 36, 43 and 53 are not directly comparable due to differences in the size of the study sample and measure of affective symptoms at each age; however broad trends can be identified.

Unadjusted associations

The unadjusted Kaplan Meier graphs showed that across all ages the influence of affective symptoms on mortality persists over many years (see figures 4.3.3.2-5); this was most evident at age 13-15, whereby the survival curves continued to diverge after nearly fifty years of follow-up. Whilst these results do not appear to support a 'sensitive period' model, it remains unclear whether associations between affective symptoms and mortality observed in mid-late adulthood are in fact driven by chronic affective symptoms originating earlier in the life course – which is addressed in the following chapter. Depression has been shown to be a highly recurrent disorder (Rutter, 1989; Rutter et al., 1976); in the NSHD, 70% of those who had internalising disorder in adolescence go on to experience mental disorder in adulthood (Colman et al., 2007b), whereas of those who experience affective symptoms, 65% report recurrent symptoms over their lifetime.

Sex adjusted associations

At ages 13-15, 43, and 53, those who experienced severe affective symptoms had an increased risk of mortality compared to those with mild/no symptoms. Similarly, at age 36 the hazard ratio for severe symptoms was also increased (HR=1.25, 95% CI 0.94-1.66), although the association was not statistically significant, possibly due to low power. These results are largely consistent with previous studies which have demonstrated associations between mortality and affective symptoms in adolescence and mid-late adulthood (Cuijpers and Smit, 2002; Lee et al., 2006).

However, weak evidence of an association at age 36 is in contrast to previous research using NSHD data whereby Henderson et al., (2011) found that psychiatric symptoms at age 36 were strongly associated with mortality. One reason for this discrepancy is that Henderson et al., (2011) used an exposure measure that not only incorporated affective symptoms, but also symptoms of schizophrenia, substance abuse, and bipolar disorder, which all demonstrate particularly strong associations with mortality (Chang et al., 2011; Saha et al., 2007). In addition, Henderson et al., (2011) weighted their analysis to account

for the social stratification of the initial NSHD sample, which results in stronger associations. For example, if the current analyses were weighted, the sex adjusted hazard ratio for severe affective symptoms at age 36 increases to 1.43 (95% CI 1.03-1.98) (reasons for not using the NSHD weighting factor are discussed in section 3.3).

Notably, the association between severe affective symptoms and mortality appeared to be particularly strong at age 43. This could be partially explained by the nature of the PSF questionnaire, which is the only measure to ask study members to respond with respect to the previous year, opposed to last few weeks. This means the PSF has a greater window to capture instances of severe or chronic affective symptoms, compared to the PSE and GHQ-28 which assess symptoms during the preceding month only.

Across all ages, severe symptoms were more strongly associated with mortality compared to those with moderate symptoms. At ages 13-15, 36 and 43, the associations were largely consistent with a potential threshold effect, whereby the risk of mortality increased only among those experiencing severe affective symptoms. However, at age 53, there was a suggestion of an apparent dose-response relationship whereby moderate symptoms also appeared to increase the risk of mortality compared to those with no/mild symptoms, although the associations were not statistically significant probably due to low power.

A dose-response relationship between depressive symptoms and mortality was observed among other community-based studies, whereby low-levels of symptom severity increased the risk of mortality (Cuijpers and Smit, 2002; Geerlings et al., 2002; White et al., 2015). However, these studies all relied on a single measure of affective symptoms so it is not possible to tell whether moderate symptoms are a risk factor for mortality in themselves, or whether they simply capture those with an increased probability of experiencing severe or clinical level symptoms (capable of interfering with daily functioning). The threshold effect at age 43 could therefore be attributed to the PSF measure's longer window, which means it has a higher likelihood of capturing those who experience the most severe symptoms (as mentioned previously).

Across all ages, there was no evidence of a statistically significant sex interaction at any age, consistent with the majority of previous studies (Cole, 2007; White et al., 2016; Wulsin et al., 1999).

Sensitivity analyses

There was little evidence that symptoms of schizophrenia explained the association between affective symptoms and mortality; sensitivity analysis demonstrated that across all ages, the hazard ratios were unaffected by the exclusion of schizophrenia cases, possibly because of the overall low number of schizophrenia cases in the NSHD (n=27).

Similarly, there was little evidence that associations between affective symptoms and mortality were explained by violent or accidental deaths, including suicide. At ages 13/15 and 36, excluding externalising deaths actually appeared to strengthen the association; whilst at age 43 and 53, the hazard ratios for severe affective symptoms were only slightly attenuated; this shows that the association between affective symptoms and mortality is driven primarily by natural causes of death. This is consistent with many other studies which have shown that depressive symptoms appear to increase the risk of mortality across many different causes of death (Chida et al., 2008; Hemingway and Marmot, 1999; Mykletun et al., 2007).

A 3-year wash out period was included to test for reverse causality, whereby poor physical health drives affective symptoms. At ages 13/15 and 36 the inclusion of a 3-year wash-out period did not alter the association between affective symptoms and mortality, whereas at age 43 the association between severe affective symptoms and mortality was slightly strengthened. In contrast, at age 53 the hazard ratio for severe symptoms was attenuated to the extent that the association was no longer statistically significant. This could imply that the association was partially explained by reverse causality, which could be a more prominent issue at older ages when study members are increasingly likely to be in poor health. In addition, the measure of affective symptoms at age 53 (GHQ-28) is the only questionnaire to include several items to relating to physical health, for instance 'Have you recently been feeling perfectly well and in good health?', 'Have you recently felt that you were ill?''. This could create a spurious association whereby the GHQ-28 could potentially reflect somatic symptoms caused by physical disease, which could be incorrectly attributed to mental health problems.

Anxiety, depressive, and sleep disturbance symptoms

Few studies have focussed on the relationship between anxiety symptoms and mortality. Whilst some studies have reported associations similar to those observed for depression and mortality (Denollet et al., 2009; Eaker et al., 2005; Laan et al., 2011; Lee et al., 2006;

Markkula et al., 2012; Ostir and Goodwin, 2006), others have found that depression, but not anxiety, was associated with an increased risk of mortality (Holwerda et al., 2007; Mykletun et al., 2007).

In the current analyses, at ages 36 and 43, the sex adjusted associations between mortality and anxiety and depressive symptoms were very similar, and the role of anxiety and depressive symptoms also remained largely equivalent after adjustment for respective anxiety/depressive symptoms. At age 43, mutual adjustment partially attenuated the hazard ratios indicating that the effect of anxiety and depressive symptoms are not independent; a similar trend was observed at age 36 although the overall associations were considerably weaker. These findings suggest that it is appropriate to use a single affective symptom measure which combines symptoms of anxiety and depression.

The results are consistent with previous studies which have shown high comorbidity between anxiety and depressive disorders (Kessler et al., 1996; Singleton et al., 2003; Vollebergh et al., 2001). Other studies have also demonstrated that anxiety and depression appear to have similar precursors (Eaton and Ritter, 1988; Richards and Goldberg, 2010) and twin studies have found that genes implicated in depression and anxiety are completely shared between the two disorders (Kendler et al., 1992; Leonardo and Hen, 2006). Furthermore, these results support the single factor solution shown across all four affective symptom measures in the NSHD (Goldberg and Hillier, 1979; Lindelow et al., 1997; Xu et al., 2013) (as described in section 3.4.9).

At age 43, additional analyses were conducted investigating the role of sleep disturbance. There appeared to be little influence of sleep disturbance on mortality compared to symptoms of anxiety and depression, which implies that associations between affective symptoms and mortality are not driven by items relating to sleep quality.

Limitations

The predominant limitation across all analyses was low power to detect small effects, which meant that weaker associations, such as those seen for 'moderate' symptoms, could not be adequately assessed.

There was some evidence of selection bias, whereby there was greater loss-to-follow-up among those who experienced severe and moderate affective symptoms; this suggests that the associations from mid-adulthood onwards could be an underestimate.

At ages 36, 43, and 53 there was between 2.3-4.3% non-response on affective symptom measures, which could also introduce bias as it is possible that those with more severe symptoms were less inclined to respond. There was 8% non-response at ages 13-15; however affective symptoms were based on teacher-ratings and therefore unlikely to introduce systematic bias.

4.5 Summary

After adjustment for sex, severe affective symptoms appeared to increase the rate of mortality compared to those with no/mild symptoms across all ages, although at age 36 the association was not statistically significant possibly due to low power. These results do not appear to be consistent with a 'sensitive period' model, although it is possible that affective symptoms originating in early-life are driving the effects seen in adulthood. There was no evidence of a sex interaction at any time point.

At all ages, severe symptoms were more strongly associated with mortality compared to those with moderate symptoms. The hazard ratio for moderate symptoms appeared slightly raised at ages 13-15 and 53; however it is unclear whether moderate symptoms are a risk factor in themselves or are simply a marker for sub-clinical disorder.

At ages 36 and 43 years, anxiety and depressive symptoms were equally predictive of mortality, suggesting that combining these symptoms into a single measure is appropriate.

Sensitivity analysis showed that associations between affective symptoms and mortality were not explained by schizophrenia or externalising deaths. The association at age 53 was partially explained by a three-year washout period, which might suggest reverse causality with poor physical health.

The next chapter tested for an accumulation effect, to elucidate whether the associations observed at each age were independent, and will also better elucidate the role played by moderate symptoms.

5. AFFECTIVE CASE ACCUMULATION OVER THE LIFE COURSE AND MORTALITY

5.1 Chapter overview

This chapter presents the results of analyses relating primarily to objective 2.1: To investigate the association between affective symptoms and mortality with respect to affective case accumulation; and objective 3.1-7: To investigate to what extent the relationship between lifetime affective caseness and mortality can be explained by the following factors: physical health status, health behaviours, psychotropic medication use, social networks, stressful life events, and adverse childhood experiences. The following hypotheses were tested:

2.1 There will be a dose-response relationship between affective case accumulation and mortality

3.0 Physical health status, health behaviours, psychotropic medication use, social networks, stressful life events, and adverse childhood experiences will all partially explain the association between lifetime affective case accumulation and mortality

Sensitivity analyses also extend the findings from chapter 4 relating to objective 1.2: To investigate the association between affective symptoms and mortality with respect to symptom severity. The following hypothesis was tested with regard to the accumulation affective symptoms over the life course:

1.2 Severe affective symptoms will be more strongly associated with mortality compared to moderate/mild symptom

This chapter presents the imputed results of crude and sex adjusted associations between affective case accumulation and mortality, in addition to sensitivity analyses examining the role of moderate affective symptom accumulation. This is followed by the results of bivariate and sex adjusted associations between all covariates and affective case accumulation, and all covariates and mortality. Multivariable analyses are then presented where the explanatory role of each covariate is demonstrated with regard to the relationship between affective case accumulation and mortality, followed by a discussion of the results.

5.2 Methods

5.2.1 Exposure variables

The main exposure variable used in this chapter is affective case accumulation which was derived using the affective 'case' variables at ages 13-15, 36, 43, and 53 (described in detail in sections 3.4.1-7).

A variable representing lifetime accumulation of 'moderate' affective symptoms was derived by adding the total number of times study members were classified as experiencing moderate symptoms across ages 13-15, 36, 43, and 53 (described in detail in sections 3.4.1-4).

5.2.2 Outcome variable

The outcome variable is all-cause mortality (as described previously in section 3.5), with follow-up from age 53 onwards.

5.2.4 Analytical strategy

Multiple imputation

Multiple imputation was used to impute all those with missing covariate data, in addition to those who were missing a single measure of affective symptoms (reasons for imputation are discussed in section 5.2.5). Fifteen data sets were imputed using chained equations (Graham et al., 2007; Royston, 2004; White et al., 2011).

Crude and sex adjusted associations between affective case accumulation and mortality (see below) were similar in the non-imputed (original) and imputed data (see Appendices F-I for results using non-imputed data). This was expected given the similarity between the non-imputed and imputed descriptive characteristics (see table 5.3.6.1).

Note that the sample size for each level of the exposures can vary between imputed datasets, therefore the sample size (n) is not presented in descriptive characteristics.

Crude and sex adjusted analyses

Descriptive analyses of the imputed data were conducted for mortality, affective caseness at ages 13-15, 36, 43 and 53, affective symptom accumulation, and all covariates, including a comparison of the observed and imputed data. A Kaplan Meier graph was created to show the unadjusted association between affective case accumulation and mortality over-

time. Power was estimated using the non-imputed (original) data, since multiple imputation rarely leads to an increase in power (Bodner, 2008).

Cox regression models were used to examine the sex adjusted relationship between affective caseness at each age and mortality from age 53 onwards, and the sex adjusted association between affective case accumulation and mortality. Sex interaction was tested using the joint Wald test and by examining the significance level and magnitude of each interaction term. As discussed previously in section 4.2.3, sensitivity analyses involved the exclusion of schizophrenia cases and externalising deaths; however it was not informative to include a three-year wash-out period to test for reverse causality with poor physical health as the affective case accumulation measure spanned several time-points.

An additional sensitivity analysis was conducted to explore whether 'moderate' symptom accumulation was associated with mortality. Sex adjusted Cox regression was used on a sub-sample that excluded all those who were ever classified as a 'severe' case in order to isolate the role of moderate symptoms.

Bivariate analyses

Bivariate and sex adjusted associations between all exposures (covariates) and mortality were assessed using Cox regression. Continuous variables were tested for non-linearity by grouping them into categories and examining the hazard ratios. Continuous variables were divided into quintiles, with the exception of BMI and systolic blood pressure which were grouped according to established cut-points (Mancia et al., 2007; World Health Organization, 2000).

Associations between affective case accumulation and all other exposures were explored using cross-tabulation. It was not appropriate to conduct Chi-squared tests or ANOVA using imputed data; therefore an estimate of the strength of association was obtained from ordinal logistic regression using Wald tests; all models were additionally adjusted for sex.

Multivariable analyses

For multivariable analyses, covariates were categorised into eight groups; these included adult socio-demographics, health status variables, health behaviours, psychotropic medication, social networks, stressful life events, adverse childhood experiences, and other childhood factors. The impact of each group and the role of each individual covariate were assessed in turn by adding the relevant variables into a sex adjusted model. The fully

adjusted model included all covariates; variables that had little or no explanatory role after the inclusion of all other covariates were not excluded as it was possible that they formed part of a causal pathway.

Interaction terms were included in sex adjusted models for affective symptoms by sex, childhood social class, adult social class, and social support from friends. Interactions were assessed using the joint Wald test and by examining the significance level and magnitude of each interaction term.

5.2.5 Missing data and multiple imputation

Table 5.2.5.1 shows that several covariates have large amounts of missing data, particularly those which were derived across multiple time-points (please see section 3.6 for detail on how covariates were derived). Investigating explanatory pathways using a complete case approach would have therefore led to greatly underpowered results since the final study sample would have consisted of only 550 study members (1144 if excluding eating choices from selected covariates).

In addition, Cox regression analyses (not shown) demonstrated that after adjusting for sex, the association between affective caseness and mortality was different for those with and without complete covariate data, whereby associations were weaker among those with complete data. This suggests that complete-case analysis would bias results. Equally, creating separate categories for missing data could also lead to bias as this means that very different values may be grouped into the same category.

Consequently, multiple imputation was used to impute missing data for all covariates and those who were missing a single measure of affective symptoms (see table 5.2.5.1); this introduced an extra 935 study members into the analytical sample, and subsequently an additional 95 deaths (see figure 5.2.5.2) – note that the outcome (mortality) was not imputed. A larger sample made it less likely that categories contained zero mortality during adjustment for covariates, or when testing for interaction effects.

Table 5.2.5.1 Missing covariate data among those with complete affective case accumulation and mortality data (n=2066)

	Missingness	
	n	%
Sex	0	0
Adult social class	53	2.57
Education	46	2.23
Systolic blood pressure (mmHg)	36	1.74
Lung function (FEV_1)	51	2.47
Pulse rate (bpm)	49	2.37
Body mass index (kg/m^2)	21	1.02
Health conditions	24	1.16
Eating choices index	947	54.16
Smoking	24	1.16
Problem drinking	0	0
Physical activity	4	0.19
Antidepressant use	171	8.28
Anxiolytic use	178	8.62
Marital status	1	0.05
Social support	4	0.19
Stressful life events	129	6.24
Childhood social class	27	1.31
Adolescent externalising	0	0
Childhood sickness absence	355	17.18
Childhood cleanliness	141	6.82
Parental abuse	123	5.95
Parental Divorce	0	0

Note: The Eating Choices Index was a based on a five-day diet diary which had between 29-43% missingness at each wave

Table 5.5.5.2 Number of times affective symptom scores were missing at ages 13-15, 36, 43, and 53, among those with linked mortality data

Number of times missing	N
0	2,066
1	935
2	423
3	654
4	187

5.3 Results

5.3.1 Participants

Participants included all those with complete affective symptom data at a minimum three time-points, and linked National Health Service Central Register mortality data from age 53 onwards.

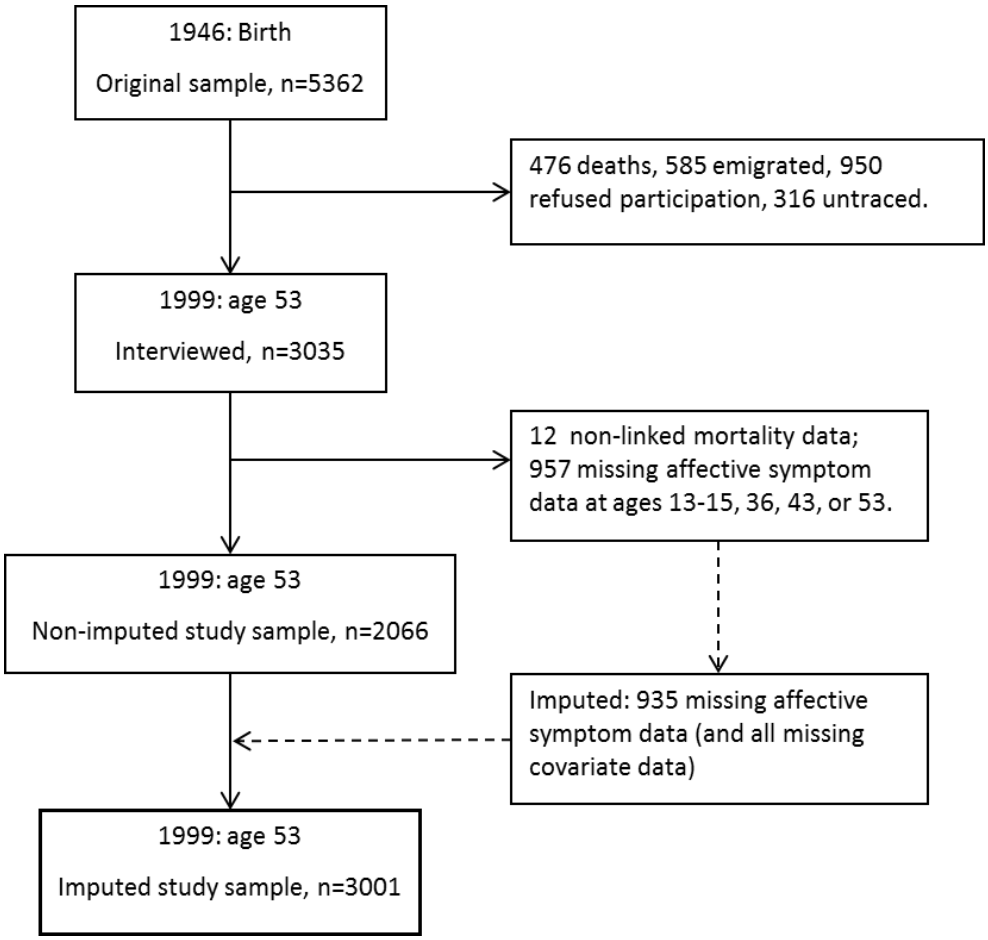

Figure 5.3.1 Participant flow from original sample to imputed study sample (see figure 4.2.4 for detailed participant flow up to those interviewed at age 53)

5.3.2 Descriptive characteristics of mortality

Follow-up time was from age 53 (1999) to mortality, or censored due to emigration or end October 2014. Mean follow-up was 14.4 years (range 0.08-15.0), during which there were 235 deaths (102 male and 133 female). See Appendix G for a comparison between non-imputed and imputed mortality descriptives by affective case accumulation.

5.3.3 Descriptive characteristics of affective case accumulation by sex

Table 5.3.3 shows the proportion of the sample that was an affective case at each age. Across all ages, females were considerably more likely to be an affective case than males.

Table 5.3.3 Descriptive characteristics for affective caseness by sex at age 13-15, 36, 43 and 53 (n=3001)

		All	Males	Females
		%	%	%
Affective case				
Age 13-15				
	No	85.1	87.6	82.7
	Yes	14.9	12.4	17.3
Age 36				
	No	83.9	88.3	79.7
	Yes	16.1	11.7	20.3
Age 43				
	No	84.4	88.3	80.6
	Yes	15.6	11.7	19.4
Age 53				
	No	83.4	88.4	78.5
	Yes	16.6	11.6	21.5

5.3.4 Sex adjusted associations between affective caseness at ages 13-15, 36, 43, and 53 and mortality from age 53 onwards

Table 5.3.4 shows that being an affective case at ages 13-15, 43, or 53 was associated with an increased risk of mortality from age 53 onwards, compared to those who were not a case. At age 36, being an affective case also appeared to increase the risk of mortality, although the association was not statistically significant. Across all ages, affective caseness appeared to increase the risk of mortality (ranging from 28-76%), suggesting that it was reasonable to test for an accumulation effect.

Table 5.3.4 Sex adjusted hazard ratios for the association between affective symptom 'caseness' at ages 13-15, 36, 43, and 53 and mortality from age 53 years, based on 3001 study members, 235 deaths and 15 imputations

		Hazard ratio (95% CI)
		Sex adjusted
Affective case		
Age 13-15		
	No	ref
	Yes	1.52 (1.08, 2.15)*
Age 36		
	No	ref
	Yes	1.28 (0.91, 1.80)
Age 43		
	No	ref
	Yes	1.76 (1.29, 2.39)**
Age 53		
	No	ref
	Yes	1.55 (1.10, 2.20)*

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

5.3.5 Descriptive characteristics for affective case accumulation

5.3.5.1 Descriptive characteristics of affective case accumulation by sex

Table 5.3.5.1 shows that 43.7% of the sample were an affective case at least once, and that females were considerably more likely to be a case than males. Females were also approximately 2.5 times more likely to have been an affective case 3-4 times.

Table 5.3.5.1 Descriptive characteristics of affective case accumulation by sex

	All (n=3001)	**Males** (n=1492)	**Females** (n=1509)
Affective case	%	%	%
0	56.3	64.5	48.3
1	29.5	26.4	32.6
2	9.6	6.5	12.6
3-4	4.6	2.6	6.6

5.3.6 Descriptive characteristics comparing the non-imputed and imputed data

Tables 5.3.6.1 and 5.2.6.2 compare the descriptive characteristics for observed (non-imputed) and imputed data (for a full list of individual variables used in the imputation model and the percentage of each variable imputed, please refer to Appendix J).

Table 5.5.6.1 shows that the imputed and observed (non-imputed) characteristics are broadly similar, although the imputed sample appears to have a higher level of affective caseness, physical inactivity, and anxiolytic use, and poorer diet scores. These differences are in the expected direction since those who are least advantaged and least healthy show the highest risk of attrition in longitudinal studies, in addition to systematic item-level missingness (Power and Elliott, 2006; Stafford et al., 2013).

Table 5.3.6.1 Descriptive characteristics of the observed (n=2006) and imputed data (n=3001)

	Non-imputed (%)	Imputed (%)
Affective symptom case[a]		
0	57.8	56.3
1	29.1	29.5
2	8.8	9.6
3-4	4.3	4.6
Sex		
Male	49.7	49.7
Female	50.3	50.3
Social class (adult)		
Professional (I)	10.6	10.2
Intermediate (II)	39.6	38.8
Skilled, non-manual (III-NM)	12.2	12.2
Skilled, manual (III-M)	25.0	25.6
Partly skilled (IV)	9.1	9.5
Unskilled (V)	3.5	3.7
Education		
None	36.6	36.6
O-level or equivalent	28.4	28.4
A-level or equivalent	25.5	25.5
Higher education	9.6	9.5
Systolic blood pressure (mmHg)		
Mean (SD)	137.6 (20.9)	137.8 (21.02)
Lung function (FEV_1)		
Mean (SD)	2.70 (0.71)	2.70 (0.72)
Pulse rate (bpm)		
Mean (SD)	68.1 (11.53)	68.3 (11.60)
Body mass index (kg/m2)		
Mean (SD)	27.5 (4.78)	27.5 (4.79)
Health conditions		
0	48.8	48.2
1	30.3	30.3
2	13.7	13.9
3+	7.3	7.6
Diet (ECI)[a]		
Mean (SD)	8.81 (1.37)	8.56 (1.43)

Smoking history		
Never smoked	28.5	28.4
Predominantly non-smoker	34.1	34.1
Predominantly smoker	21.6	21.6
Lifetime smoker	15.8	15.8
Problem drinking		
No	88.6	88.6
Yes	11.4	11.4
Physical activity[a]		
Inactive	18.6	19.2
Moderately active	46.8	46.7
Most active	34.6	34.1
Antidepressant use		
No	90.9	90.0
Yes	9.2	10.0
Anxiolytic use		
No	92.8	91.5
Yes	7.2	8.5
Marital status		
Married or cohabiting	79.2	78.7
Single	5.0	5.4
Divorced, widowed, separated	15.7	15.9
Social support (friends)[a]		
Always	82.3	81.8
Often/Sometimes/ Never	17.7	18.2
Stressful life events		
0-5	55.8	55.5
6-9	33.4	33.3
10+	10.8	11.3
Social class (childhood)		
Professional (I)	6.2	6.2
Intermediate (II)	19.4	19.5
Skilled, non-manual (III-NM)	16.3	16.4
Skilled, manual (III-M)	33.0	32.9
Partly skilled (IV)	19.0	18.8
Unskilled (V)	6.1	6.1
Externalising (age 13-15)		
None/mild	76.9	76.6
Moderate	16.6	17.0
Severe	6.6	6.4

Childhood sickness absence (weeks)		
0-4	52.9	53.1
4-10	36.3	36.0
10+	10.9	11.0
Cleanliness of child		
Amongst the best/ average	97.7	97.4
Amongst the worst	2.3	2.6
Parental abuse		
No	94.1	93.7
Yes	5.9	6.3
Parental divorce		
No	94.7	94.7
Yes	5.3	5.3

a: Variables derived following the imputation process using measures at multiple time-points

Table 5.5.6.2 shows a further breakdown of affective case accumulation by the timing of affective caseness. Within each level of affective case accumulation, the timing of affective caseness appears to be distributed relatively evenly.

Table 5.3.6.2 Descriptive characteristics of the timing of affective caseness by affective case accumulation, for non-imputed and imputed data, based on 15 imputations

		Non-imputed data (n=2066)		Imputed data (n=3001)
Affective caseness	**Timing of case[a]**	**n**	**%**	**%**
0	0000	1,195	57.8	56.3
1	0001	172	8.3	7.4
	0010	124	6.0	6.3
	0100	140	6.8	7.0
	1000	165	8.0	8.8
2	0011	37	1.8	2.0
	0101	32	1.6	1.9
	0110	37	1.8	2.1
	1001	29	1.4	1.4
	1010	26	1.3	1.2
	1100	21	1.0	1.0
3-4	0111	39	1.9	2.2
	1011	12	0.6	0.6
	1101	12	0.6	0.6
	1110	15	0.7	0.7
	1111	10	0.5	0.6

a: 1 = presence of an affective case at age 13-15, 36, 43, or 53, respectively

5.3.7 Power analyses for the association between affective case accumulation and mortality

Table 5.3.7 shows that there was adequate power to detect hazard ratios greater than 1.6 for those who were a case once. For those who were a case 2-4 times, there was reasonable power to detect hazard ratios in the region of 2.0-2.5 only. Across all levels of affective case accumulation, there was a high chance of type II error for detecting hazard ratios less than 1.4. Note that power calculations are estimated using the non-imputed data.

Table 5.3.7 Power for affective case accumulation based on a 5.2% risk of all-cause mortality among those who were never a case, and alpha 0.05 (n=2066)

	Power (%)		
	1 (n=601)	**2 (n=182)**	**3-4 (n=88)**
Hazard ratio			
1.2	14.6	8.3	5.9
1.4	42.3	20.9	13.1
1.6	73.2	39.9	23.8
1.8	91.9	61.3	40.0
2.0	98.4	79.4	53.8
2.5	100.0	98.3	86.0

5.3.8 Crude and sex adjusted associations between affective case accumulation and mortality

Figure 5.3.8 shows that study members who were an affective case 3-4 times had the lowest survival probability, whilst those who were never a case had the highest survival probability.

There appears to be a dose-response relationship up until approximately ten years of follow-up, at which point the survival curves for those who were a case one or two times begin to converge and after 13 years of follow-up the survival probabilities are very similar.

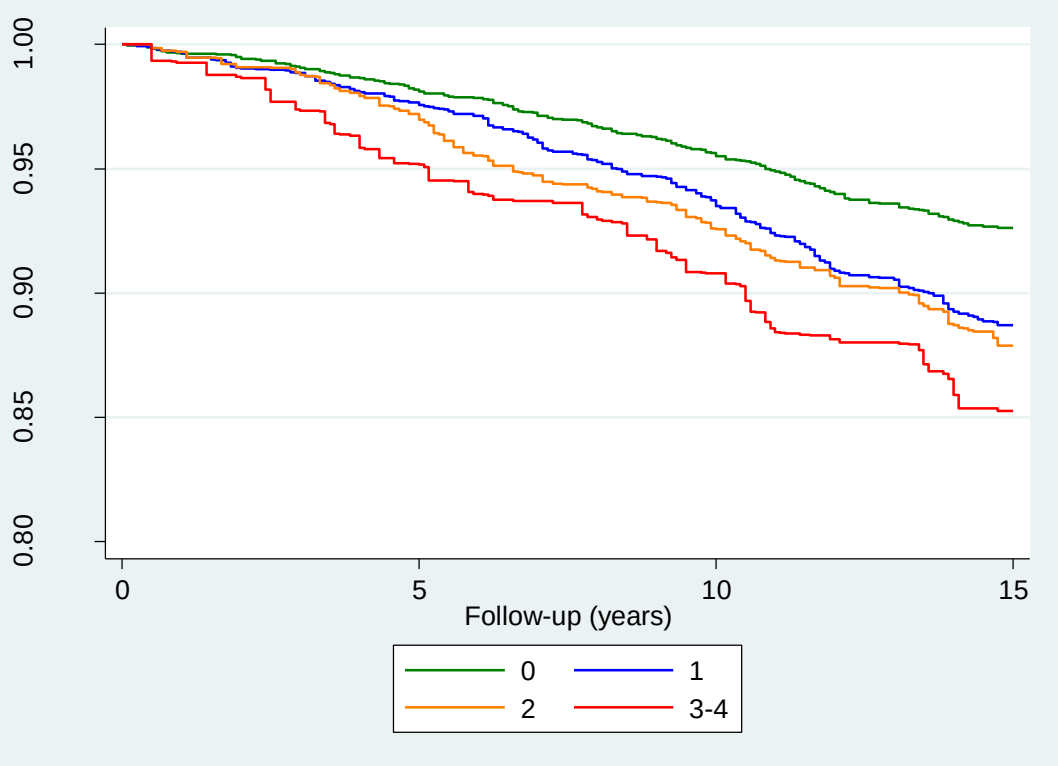

Figure 5.3.8 Unadjusted Kaplan-Meier survival curves for all-cause mortality by lifetime affective caseness; based on 235 deaths and 15 imputations (n=3001)

Table 5.3.8.1 shows that after adjustment for sex, there was an apparent dose-response relationship between affective caseness and mortality, whereby the risk of mortality increased as caseness increased.

Among males, there was no evidence of an association between those who were a case 3-4 times and mortality, likely due to inadequate power. All sex interaction terms were not statistically significant (p>0.3). There was no evidence that the proportional hazards assumption was violated among unadjusted or sex adjusted associations.

Table 5.3.8.1 Sex adjusted hazard ratios for the association between affective caseness and mortality; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)		
	Sex adjusted	Males (n=1492)	Females (n=1509)
Affective case			
0	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.70 (1.14, 2.53)*	1.86 (1.14, 3.02)*
2	1.87 (1.18, 2.97)*	2.15 (1.16, 3.99)*	1.70 (0.87, 3.29)
3-4	2.34 (1.36, 4.04)*	1.07 (0.27, 4.26)	3.19 (1.69, 6.04)**

*p<0.05

**p<0.001

Table 5.3.8.2 shows that after adjustment for sex, the hazard ratio for those were an affective case 2 times was slightly attenuated after excluding cases of schizophrenia. Excluding externalising deaths had no effect on the hazard ratios.

Table 5.3.8.2 Sex adjusted hazard ratios for the association between lifetime affective caseness and mortality, excluding schizophrenia cases and excluding externalising deaths, based on 15 imputations

	Hazard ratio (95% CI)		
	Sex adjusted (n=3001, 235 deaths)	**+ excluding schizophrenia** (n=2984, 231 deaths)	**+ excluding externalising** deaths (n=2981, 215 deaths)
Affective caseness			
0	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.75 (1.29, 2.38)**	1.73 (1.26, 2.39)*
2	1.87 (1.18, 2.97)*	1.74 (1.08, 2.81)*	1.87 (1.17, 2.97)*
3-4	2.34 (1.36, 4.04)*	2.30 (1.31, 4.03)*	2.33 (1.32, 4.10)*

* $p < 0.05$

**$p < 0.001$

5.3.9 Sex adjusted associations between moderate affective symptom accumulation and mortality

Table 5.3.9 shows the sex adjusted associations between mortality and the number of times a person experienced moderate symptoms. Although power is low, the hazard ratios show no evidence that moderate symptoms increased the risk of mortality compared to those who only ever experienced no/mild symptoms.

Table 5.3.9 Sex adjusted hazard ratios for the association between lifetime moderate symptom accumulation and mortality from age 53 onwards, based on 1682 study members and 102 deaths

	Sex adjusted Hazard ratio (95% CI)
Moderate symptom case	
0	ref
1	0.78 (0.43, 1.41)
2	0.90 (0.49, 1.62)
3-4	1.01 (0.51, 1.99)

Note: The analytical sample excluded all those who ever experienced a severe case

5.3.10 Crude and sex adjusted associations between affective case accumulation and all other exposures

Table 5.3.10 shows that there were statistically strong ($p<0.001$) crude or sex adjusted associations between affective case accumulation and sex, adult social class, lung function, number of self-reported health conditions, physical activity levels, antidepressant use, anxiolytic use, marital status, social support, stressful life events, and parental abuse. More moderate ($p<0.05$) associations were observed with respect to systolic blood pressure, smoking, problem drinking, eating choices, parental divorce, childhood cleanliness, and childhood sickness absence, whilst slightly weaker associations were observed with regard to pulse rate, BMI, and externalising behaviour. Although not statistically significant, the relationship between affective case accumulation and BMI appeared stronger among women (not shown), as shown previously in the NSHD (Gaysina et al., 2011). Adjustment for sex appeared to strengthen associations between affective case accumulation and smoking, problem drinking, eating choices, and childhood cleanliness, but had relatively little impact across all other covariates.

There appears to be dose-response relationships between affective case accumulation and sex (female), pulse rate, BMI, number of health conditions, smoking, problem drinking, anxiolytic use, antidepressant use, number of stressful life events, parental abuse, and childhood sickness absence. Inverse dose-response relationships were observed with respect to lung function, systolic blood pressure, physical activity levels, healthy eating choices, and perceived social support; an inverse association between affective symptoms and systolic blood pressure has previously been observed in the NSHD data (Tikhonoff et al., 2014).

Study members who were ever an affective case appear less likely to be in higher social classes, compared to those who were never a case. Those who were never a case demonstrate the highest level of education, whilst those who were a case 3-4 times were most likely to have no qualifications. Study members who were an affective case 2 or more times had a higher likelihood of being 'divorced, widowed or separated', and a higher likelihood of being 'amongst the worst' for childhood cleanliness. Those who were a case 3-4 times also appeared considerably more likely to have experienced parental divorce, parental abuse, and severe externalising behaviour in adolescence.

Childhood social class was the only variable to show no evidence of an association with affective case accumulation.

Table 5.3.10 Crude and sex adjusted associations between affective case accumulation and all exposures, based on 15 imputations (n=3001)

	%					
Exposure	**0**	**1**	**2**	**3-4**	**P[a]**	**p[b]**
Sex						
Male	56.9	44.5	33.9	28.1	<0.001	-
Female	43.1	55.5	66.1	71.9		
Social class (adult)						
Professional (I)	11.3	9.5	6.4	9.3	<0.001	<0.001
Intermediate (II)	41.9	35.0	34.7	33.4		
Skilled, non-manual (III-NM)	10.6	13.9	16.5	11.3		
Skilled, manual (III-M)	25.1	27.6	22.5	25.6		
Partly skilled (IV)	8.3	9.6	14.2	13.7		
Unskilled (V)	2.8	4.5	5.6	6.7		
Education						
None	34.0	39.8	37.8	45.9	<0.001	0.008
O-level or equivalent	28.0	27.7	32.2	31.1		
A-level or equivalent	27.2	25.2	21.2	15.7		
Higher education	10.9	7.4	8.8	7.2		
Systolic blood pressure (mmHg)						
Mean (SD)	137.4 (19.8)	135.2 (20.1)	134.5 (19.7)	130.6 (18.3)	0.001	0.08
Lung function (FEV_1)						
Mean (SD)	2.81 (0.70)	2.63 (0.72)	2.44 (0.70)	2.36 (0.64)	<0.001	<0.001
Pulse rate (bpm)						
Mean (SD)	68.0 (11.4)	68.5 (11.8)	68.7 (11.7)	69.4 (12.5)	0.10	0.06
Body mass index (kg/m2)						
Mean (SD)	27.4 (4.5)	27.5 (5.0)	27.7 (5.5)	28.1 (5.4)	0.08	0.08
Health conditions						
0	54.4	43.6	36.4	26.2	<0.001	<0.001
1	28.6	33.2	31.7	30.1		
2	11.4	14.9	19.3	26.3		
3 or more	5.5	8.3	12.6	17.4		
Smoking						
Never smoked	29.5	29.5	22.5	21.2	0.01	0.002
Predominantly non-smoker	35.1	33.2	33.6	28.8		
Predominantly smoker	20.7	21.2	25.9	26.1		
Lifetime smoker	14.7	16.1	18.1	24.0		
Problem drinking						
No	89.2	89.0	86.4	82.9	0.08	0.003
Yes	10.8	11.0	13.6	17.1		

Physical activity						
Inactive	16.2	20.7	26.8	29.8	<0.001	<0.001
Least active	46.4	46.4	47.4	50.4		
Most active	37.4	32.8	25.8	19.7		
Eating choices (ECI)						
Mean (SD)	8.61 (1.41)	8.54 (1.44)	8.45 (1.40)	8.37 (1.57)	0.04	0.001
Antidepressant use						
No	95.5	88.0	77.1	62.2	<0.001	<0.001
Yes	4.5	12.0	22.9	37.8		
Anxiolytic use						
No	95.8	90.6	81.0	67.5	<0.001	<0.001
Yes	4.2	9.4	19.0	32.5		
Marital status						
Married or cohabiting	81.5	77.8	68.4	71.3	<0.001	<0.001
Single	4.6	6.8	6.3	5.2		
Divorced, widowed, separated	13.9	15.4	25.3	23.5		
Social support (friends)						
Always	85.0	80.9	74.6	64.3	<0.001	<0.001
Often, sometimes, or never	15.0	19.2	25.5	35.7		
Stressful Life events						
0-5	63.5	51.5	35.6	25.2	<0.001	<0.001
6-9	30.2	36.2	39.0	39.9		
10+	6.4	12.3	25.4	34.9		
Parental divorce						
No	95.4	94.8	95.6	85.0	0.01	0.01
Yes	4.6	5.2	4.4	15.0		
Cleanliness of child						
Amongst the best / average	98.0	97.3	94.9	96.2	0.02	0.004
Amongst the worst	2.0	2.8	5.1	3.8		
Parental abuse						
No	95.5	93.2	90.6	81.6	<0.001	<0.001
Yes	4.5	6.8	9.4	18.4		
Social class (childhood)						
Professional (I)	6.6	4.5	7.6	10.2	0.63	0.64
Intermediate (II)	20.3	18.7	20.1	14.3		
Skilled, non-manual (III-NM)	16.2	17.7	12.4	18.7		
Skilled, manual (III-M)	33.3	31.4	34.8	34.2		
Partly skilled (IV)	18.2	20.6	17.6	18.3		
Unskilled (V)	5.4	7.2	7.4	4.4		

Adolescent externalising						
Mild	77.0	77.3	76.3	68.7	0.08	0.05
Moderate	17.3	16.5	16.0	18.1		
Severe	5.7	6.2	7.7	13.3		
Childhood sickness absence (weeks)						
0-4	54.8	52.2	47.5	48.9	0.004	0.006
4-10	35.8	35.5	39.3	33.9		
10+	9.4	12.4	13.2	17.2		

a: Wald test/joint Wald test p value using ordinal logistic regression (unadjusted)

b: Wald test/joint Wald test p value using ordinal logistic regression (sex adjusted)

5.3.11 Crude and sex adjusted associations between all exposures and mortality

Table 5.3.11 shows that in both crude and sex adjusted models, there was an apparent dose-response relationship between affective case accumulation and mortality, as previously described in detail.

There were statistically strong ($p<0.001$) crude or sex adjusted associations between mortality and lung function, pulse-rate, number of health conditions, smoking, physical activity, eating choices, anxiolytic use, and marital status. More moderate associations ($p<0.05$) were observed with respect to sex, adult social class, education, BMI, problem drinking, antidepressant use, childhood social class, adolescent externalising, and childhood sickness absence.

The hazard ratios indicated several possible dose-response relationships between mortality and pulse rate, BMI, health conditions, and smoking (continuous variables were tested for linearity). Inverse dose-response relationships were seen with respect to adult social class, lung function, physical activity, dietary score (ECI), and to an extent, childhood social class.

An increased risk of mortality was also associated with being male, problem drinking, severe adolescent externalising, and 10+ weeks of sickness absence. Compared to those who were married, being singe was more strongly associated with an increased risk of mortality than those who were 'divorced, separated or widowed'. Study members who were educated to A-level equivalent or higher appeared to show a reduced risk of mortality compared to those with lower levels of education.

Although the associations were not statistically significant, increased systolic blood pressure, not always having social support from friends, ten or more stressful life events, parental divorce, being rated amongst the worst for childhood cleanliness, and parental abuse, all appeared to raise the hazard ratio for mortality.

Adjustment for sex appeared to strengthen associations for affective case accumulation and lung function, and to a lesser extent adult social class (partly skilled and unskilled), number of health conditions (two or more), and psychotropic medication use. This is because females had a lower risk of mortality, but a higher risk of affective symptoms, poorer lung function, were more likely to be party-skilled or unskilled social class, and have a greater number of health conditions. Adjustment for sex appeared to partially explain the association between education (higher level) and mortality, as fewer females reported

higher level qualifications. There was no notable difference between the unadjusted and sex adjusted associations across all other exposure variables.

Table 5.3.11 Crude and sex adjusted hazard ratios for the association between mortality and all exposures, based on 235 deaths and 15 imputations (n=3001)

	Mortality Hazard Ratio (95% CI)	
	Unadjusted	**Sex adjusted**
Affective symptoms		
0	ref	ref
1	1.67 (1.24, 2.26)*	1.76 (1.29, 2.38)**
2	1.70 (1.08, 2.68)*	1.87 (1.18, 2.97)*
3-4	2.08 (1.22, 3.57)*	2.34 (1.36, 4.04)*
Sex		
Male	ref	-
Female	0.75 (0.58, 0.97)*	-
Adult social class		
Professional (I)	ref	ref
Intermediate (II)	0.93 (0.53, 1.64)	0.96 (0.55, 1.69)
Skilled, non-manual (III-NM)	0.96 (0.49, 1.87)	1.01 (0.51, 1.99)
Skilled, manual (III-M)	1.54 (0.89, 2.66)	1.56 (0.90, 2.70)
Partly skilled (IV)	1.82 (0.97, 3.41)	1.91 (1.02, 3.59)*
Unskilled (V)	2.02 (0.94, 4.33)	2.19 (1.01, 4.73)*
Education		
None	ref	ref
O-level or equivalent	0.87 (0.64, 1.20)	0.91 (0.66, 1.24)
A-level or equivalent	0.63 (0.44, 0.89)*	0.62 (0.43, 0.88)*
Higher education	0.74 (0.45, 1.21)	0.68 (0.42, 1.12)*
Systolic blood pressure (mmHg)		
Per standard deviation	1.13 (0.97, 1.31)	1.10 (0.95, 1.28)
Lung function (FEV_1)		
Per litre	0.66 (0.54, 0.80)**	0.45 (0.36, 0.56)**
Pulse rate (bpm)		
Per standard deviation	1.52 (1.34, 1.73)**	1.51 (1.33, 1.72)**
Body mass index (kg/m^2)		
Per standard deviation	1.17 (1.03, 1.34)*	1.18 (1.03, 1.35)
Health conditions		
0	ref	ref
1	1.24 (0.87, 1.77)	1.26 (0.88, 1.80)
2	1.93 (1.31, 2.84)*	2.03 (1.37, 2.99)**
3 or more	2.72 (1.68, 4.38)**	2.83 (1.75, 4.59)**

Smoking		
Never smoked	ref	ref
Predominantly non-smoker	1.28 (0.85, 1.92)	1.25 (0.82, 1.87)
Predominantly smoker	2.14 (1.43, 3.20)**	2.09 (1.39, 3.12)**
Lifetime smoker	3.39 (2.30, 5.02)**	3.33 (2.25, 4.92)**
Problem drinking		
No	ref	ref
Yes	1.49 (1.05, 2.12)*	1.42 (1.00, 2.03)
Physical activity		
Inactive	ref	ref
Least active	0.54 (0.40, 0.74)**	0.53 (0.39, 0.72)**
Most active	0.37 (0.26, 0.53)**	0.35 (0.24, 0.50)**
Eating Choices Index		
Per unit	0.78 (0.69, 0.88)**	0.79 (0.69, 0.89)**
Antidepressant use		
No	ref	ref
Yes	1.64 (1.07, 2.52)*	1.76 (1.13, 2.70)*
Anxiolytic use		
No	ref	ref
Yes	1.96 (1.35, 2.87)**	2.04 (1.39, 2.99)**
Marital status		
Married or cohabiting	ref	ref
Single	2.32 (1.47, 3.68)**	2.27 (1.43, 3.60)*
Divorced, widowed, separated	1.40 (0.97, 2.03)	1.45 (1.00, 2.10)*
Social support (friends)		
Always	ref	Ref
Often/sometimes/never	1.31 (0.95, 1.81)	1.27 (0.92, 1.75)
Stressful life events		
0-5	ref	ref
6-9	0.96 (0.70, 1.33)	0.98 (0.71, 1.35)
10+	1.28 (0.81, 2.04)	1.32 (0.82, 2.10)
Parental divorce		
No	ref	ref
Yes	1.33 (0.80, 2.22)	1.35 (0.81, 2.23)
Childhood cleanliness		
Amongst the best/average	ref	ref
Amongst the worst	1.97 (0.97, 4.00)	1.89 (0.94, 3.84)
Parental abuse		
No	ref	ref
Yes	1.28 (0.77, 2.12)	1.31 (0.79, 2.18)

Childhood social class		
Professional (I)	ref	ref
Intermediate (II)	2.14 (0.91, 5.03)	2.13 (0.91, 5.01)
Skilled, non-manual (III-NM)	2.03 (0.86, 4.81)	2.03 (0.86, 4.82)
Skilled, manual (III-M)	2.34 (1.02, 5.35)*	2.34 (1.03, 5.36)*
Partly skilled (IV)	3.01 (1.30, 6.95)*	3.02 (1.31, 6.99)*
Unskilled (V)	2.97 (1.18, 7.47)*	2.96 (1.18, 7.44)*
Adolescent externalising		
Mild	ref	ref
Moderate	1.05 (0.72, 1.55)	1.03 (0.70, 1.51)
Severe	1.73 (1.10, 2.73)*	1.71 (1.09, 2.69)*
Childhood sickness absence (weeks)		
0-4	ref	ref
4-10	1.08 (0.78, 1.49)	1.08 (0.78, 1.50)
10+	1.93 (1.30, 2.84)*	1.94 (1.32, 2.86)**

* $p < 0.05$

**$p < 0.001$

5.3.12 Multivariable adjusted associations between affective case accumulation and mortality

All covariates were included in multivariable analyses as in this chapter, and chapter 6, nearly all demonstrated an association with affective case accumulation and mortality – even if not statistically significant. Furthermore, it is possible that variables which do not have an association with the main outcome and exposure can still act as a confounder or mediator in multivariable models as a result of a suppression effect.

Tables 5.3.12.1-9 shows the impact of each individual covariate and each group of covariates on the sex adjusted association between affective case accumulation and mortality; all multivariable models were based on 235 deaths, n=3001 and 15 imputations.

Table 5.3.12.1 shows that the sex adjusted hazard ratios were slightly attenuated after adjustment for socio-demographic variables, although all associations remained statistically significant. Adult social class largely accounts for the attenuation, whilst education appeared to have a minimal effect.

Table 5.3.12.2 indicates that the sex adjusted hazard ratios were partially attenuated after adjustment for al health status variables, whereby the hazard ratios were no longer significant among those who were a case 2 or more times. The variables which most strongly accounted for this attenuation included lung function and the number of self-reported health conditions, whilst pulse rate also attenuated the association among those who were a case 3-4 times. The hazard ratios were largely unaffected by systolic blood pressure and BMI; these variables had no influence on the hazard ratios if lung function, health conditions, and pulse rate were included in the model.

Table 5.3.12.3 shows that the sex adjusted hazard ratios were partially attenuated after adjustment for all health behaviour variables, whereby the hazard ratio was no longer statistically significant for those who were a case 2 times. The variables which most strongly accounted for the attenuation were physical activity and lifetime smoking. Problem drinking appeared to have little influence on the hazard ratios, even after adjustment for adult social class (not shown).

Table 5.3.12.4 shows that the sex adjusted hazard ratios were partially attenuated after adjustment for psychotropic medication variables, whereby the hazard ratios were no longer statistically significant for those who were a case 2 or 3-4 times. Both anxiolytic use and antidepressant use appeared to contribute to the attenuation.

Table 5.3.12.5 shows that the sex adjusted hazard ratios were slightly attenuated after adjustment for social network variables, although all associations remained statistically significant. This attenuation was largely accounted for by marital status, while social support had relatively little impact on the hazard ratios.

An interaction between affective caseness and social support was tested as high levels of social support have been shown to buffer the effect of depression on mortality in myocardial infarction patients (Frasure-Smith et al., 2000); however there was no evidence of an interaction in the current analyses (all interaction terms $p>0.05$). If anything, the hazard ratios suggested the association between affective case accumulation and mortality was stronger among those who had the highest levels of perceived support from friends.

Table 5.3.12.6 shows that the sex adjusted hazard ratios were unaffected by adjustment for stressful life events.

Table 5.3.12.7 shows that the sex adjusted hazard ratios were largely unaffected by adjustment for all adverse childhood experience variables, apart from a slight reduction in the hazard ratio among those who were a case 3-4 times. Controlling individually for childhood cleanliness, parental abuse, or divorce had no notable impact on the hazard ratios.

Table 5.3.12.8 shows that the sex adjusted hazard ratios demonstrated only a very slight attenuation after adjustment for other childhood factors. Childhood social class, adolescent externalising, and childhood sickness absence had little influence on the hazard ratios.

Table 5.3.12.1 Hazard ratios for the association between affective case accumulation and mortality, adjusted for socio-economic variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)			
	Sex adjusted	Sex + adult social class	Sex + education	All
Affective Case				
0	ref	ref	Ref	ref
1	1.76 (1.29, 2.38)**	1.70 (1.25, 2.31)*	1.73 (1.27, 2.34)**	1.71 (1.26, 2.33)*
2	1.87 (1.18, 2.97)*	1.77 (1.12, 2.79)*	1.85 (1.17, 2.94)*	1.78 (1.13, 2.83)*
3-4	2.34 (1.36, 4.04)*	2.19 (1.26, 3.78)*	2.25 (1.31, 3.89)*	2.16 (1.25, 3.74)*

* $p < 0.05$

**$p < 0.001$

Table 5.3.12.2 Hazard ratios for the association between affective case accumulation and mortality, adjusted for health status variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)						
	Sex adjusted	Sex + Systolic blood pressure	Sex + Lung function	Sex + Pulse rate	Sex + Body mass index	Sex + health conditions	All
Affective case							
0	ref	ref	ref	ref	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.77 (1.31, 2.41)**	1.66 (1.22, 2.27)*	1.71 (1.26, 2.32)*	1.75 (1.29, 2.37)**	1.66 (1.22, 2.25)*	1.58 (1.16, 2.15)*
2	1.87 (1.18, 2.97)*	1.88 (1.19, 2.98)*	1.62 (1.02, 2.56)*	1.83 (1.16, 2.89)*	1.84 (1.16, 2.92)*	1.65 (1.04, 2.60)*	1.50 (0.95, 2.36)
3-4	2.34 (1.36, 4.04)*	2.41 (1.40, 4.14)*	2.01 (1.16, 3.49)*	2.17 (1.26, 3.75)*	2.29 (1.33, 3.96)*	1.91 (1.10, 3.34)*	1.63 (0.93, 2.88)

* $p < 0.05$

**$p < 0.001$

Table 5.3.12.3 Hazard ratios for the association between affective case accumulation and mortality, adjusted for health behaviour variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)					
	Sex adjusted	Sex + diet	Sex + lifetime smoking	Sex + problem drinking	Sex + physical activity	All
Affective case						
0	ref	ref	ref	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.71 (1.26, 2.31)*	1.72 (1.26, 2.34)*	1.75 (1.29, 2.38)**	1.67 (1.23, 2.27)*	1.66 (1.22, 2.27)*
2	1.87 (1.18, 2.97)*	1.76 (1.12, 2.79)*	1.72 (1.09, 2.73)*	1.84 (1.16, 2.91)*	1.65 (1.04, 2.62)*	1.55 (0.98, 2.47)
3-4	2.34 (1.36, 4.04)*	2.12 (1.21, 3.70)*	2.01 (1.16, 3.48)*	2.27 (1.32, 3.92)*	2.02 (1.17, 3.51)*	1.76 (1.01, 3.07)*

* $p < 0.05$

**$p < 0.001$

Table 5.3.12.4 Hazard ratios for the association between affective case accumulation and mortality, adjusted for psychotropic medication variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)			
	Sex adjusted	Sex + anxiolytic use	Sex + antidepressant use	All
Affective Case				
0	ref	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.70 (1.25, 2.31)*	1.71 (1.26, 2.31)*	1.67 (1.23, 2.27)*
2	1.87 (1.18, 2.97)*	1.71 (1.07, 2.72)*	1.74 (1.10, 2.77)*	1.65 (1.03, 2.63)
3-4	2.34 (1.36, 4.04)*	1.96 (1.11, 3.46)*	2.07 (1.16, 3.69)*	1.85 (1.03, 3.34)

* $p < 0.05$

**$p < 0.001$

Table 5.3.12.5 Hazard ratios for the association between affective case accumulation and mortality, adjusted for social network variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)			
	Sex adjusted	Sex + marital status	Sex + social support	All
Affective Case				
0	ref	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.71 (1.25, 2.33)*	1.74 (1.28, 2.37)**	1.70 (1.25, 2.31)*
2	1.87 (1.18, 2.97)*	1.77 (1.12, 2.81)*	1.84 (1.16, 2.92)*	1.74 (1.09, 2.78)*
3-4	2.34 (1.36, 4.04)*	2.24 (1.30, 3.86)*	2.26 (1.30, 3.92)*	2.17 (1.25, 3.77)*

* $p < 0.05$

**$p < 0.001$

Table 5.3.12.6 Hazard ratios for the association between affective case accumulation and mortality, adjusted for stressful life events; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)	
	Sex adjusted	Sex + stressful life events
Affective Case		
0	ref	ref
1	1.76 (1.29, 2.38)**	1.76 (1.29, 2.40)**
2	1.87 (1.18, 2.97)*	1.87 (1.16, 3.00)*
3-4	2.34 (1.36, 4.04)*	2.33 (1.33, 4.07)*

* p < 0.05
**p < 0.001

Table 5.3.12.7 Hazard ratios for the association between affective case accumulation and mortality, adjusted for adverse childhood experiences (ACEs); based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)				
	Sex adjusted	Sex + childhood cleanliness	Sex + parental abuse	Sex + parental divorce	All
Affective Case					
0	ref	ref	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.74 (1.29, 2.37)**	1.75 (1.29, 2.38)**	1.76 (1.29, 2.38)**	1.74 (1.28, 2.36)**
2	1.87 (1.18, 2.97)*	1.82 (1.15, 2.88)*	1.86 (1.18, 2.95)*	1.88 (1.19, 2.97)*	1.82 (1.15, 2.88)*
3-4	2.34 (1.36, 4.04)*	2.30 (1.33, 3.97)*	2.29 (1.32, 3.96)*	2.28 (1.32, 2.95)*	2.22 (1.27, 3.86)*

* p < 0.05
**p < 0.001

Table 5.3.12.8 Hazard ratios for the association between affective case accumulation and mortality, adjusted for other childhood factors, based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)				
	Sex adjusted	Sex + Childhood Social class	Sex + Adolescent externalising	Sex + Childhood sickness absence	All
Affective Case					
0	ref	ref	ref	ref	ref
1	1.76 (1.29, 2.38)**	1.72 (1.27, 2.33)*	1.76 (1.30, 2.39)**	1.72 (1.27, 2.34)**	1.70 (1.25, 2.30)*
2	1.87 (1.18, 2.97)*	1.87 (1.18, 2.97)*	1.85 (1.17, 2.93)*	1.83 (1.15, 2.89)*	1.82 (1.15, 2.88)*
3-4	2.34 (1.36, 4.04)*	2.38 (1.38, 4.10)*	2.25 (1.30, 3.90)*	2.24 (1.30, 3.88)*	2.22 (1.28, 3.86)*

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

Table 5.3.12.9 summarises the extent to which the sex adjusted association between affective case accumulation and mortality was explained by each group of covariates (obtained from the 'All' group hazard ratios presented in tables 5.3.12.1-8). Since each covariate group is not independent of one another, these figures provide only an approximate indication of the importance of each covariate group.

Table 5.3.12.9 shows that the association between affective case accumulation and mortality was most strongly attenuated by health status, health behaviours and psychotropic medication use. More moderate attenuation was observed with respect to social networks and adult socio-economic factors, and to a lesser extent other childhood factors and adverse childhood experiences. Stressful life events appeared to have little explanatory role.

Table 5.3.12.9 Percentage attenuation of sex adjusted associations between affective case accumulation and mortality, by each covariate group

	% attenuation[a]		
	Affective caseness		
Covariate group	**1**	**2**	**3-4**
Physical health status	23.7	42.5	53.0
Health behaviours	13.2	36.8	43.3
Psychotropic medication	11.8	25.3	36.6
Social networks	7.9	14.9	12.7
Adult socio-economic factors	6.6	10.3	13.4
Other childhood factors	7.9	5.7	9.0
Adverse childhood experiences	2.6	5.7	9.0
Stressful life events	0.0	0.0	0.7
Fully adjusted (all groups)	39.5	81.6	86.6

a: % attenuation of each group of covariates entered into the sex-adjusted model (different covariate groups were not entered into the model together)

Table 5.3.12.10 and figure 5.3.12.10 summarise the extent to which the sex adjusted association between affective case accumulation and mortality was explained by each individual covariate (obtained from the hazard ratios presented in tables 5.3.12.1-8); however, as mentioned previously, these figures should be interpreted with caution as each covariate is not independent. Table 5.3.12.10 shows that health conditions, lung function, and physical activity most strongly attenuated the association between affective case accumulation and mortality across all levels of affective caseness (>10% attenuation). Among those who were a case 2-4 times, anxiolytic use, smoking, antidepressant use, diet, and adult social class also had a relatively strong explanatory effect (>10% attenuation), and to a lesser extent marital status and pulse rate. All other covariates did not demonstrate a notable explanatory effect.

Table 5.3.12.10 Percentage attenuation of sex adjusted associations between affective case accumulation and mortality, by individual covariates (ordered by total explanatory effect)

	% attenuation[a]		
	Affective caseness		
Covariate	**1**	**2**	**3-4**
Health conditions	13.2	25.3	32.1
Lung function	13.2	28.7	24.6
Physical Activity	11.8	25.3	23.9
Anxiolytic use	7.9	18.4	28.4
Smoking	5.3	17.2	24.6
Antidepressant use	6.6	14.9	20.1
Diet	6.6	12.6	16.4
Adult Social class	7.9	11.5	11.2
Marital status	6.6	11.5	7.5
Pulse rate	6.6	4.6	12.7
Childhood Sickness Absence	5.3	4.6	7.5
Education	3.9	2.3	6.7
Social support	2.6	3.4	6.0
Childhood Cleanliness	2.6	5.7	3.0
Problem drinking	1.3	3.4	5.2
Adolescent externalising	0.0	2.3	6.7
Body mass index	1.3	3.4	3.7
Parental abuse	1.3	1.1	3.7
Parental divorce	0.0	-1.1	4.5
Childhood Social class	5.3	0.0	-3.0
Stressful life Events	0.0	0.0	0.7
Systolic blood pressure	-1.3	-1.1	-5.2

a: % attenuation of each individual covariate entered into the sex-adjusted model (different covariates were not entered into the model together)

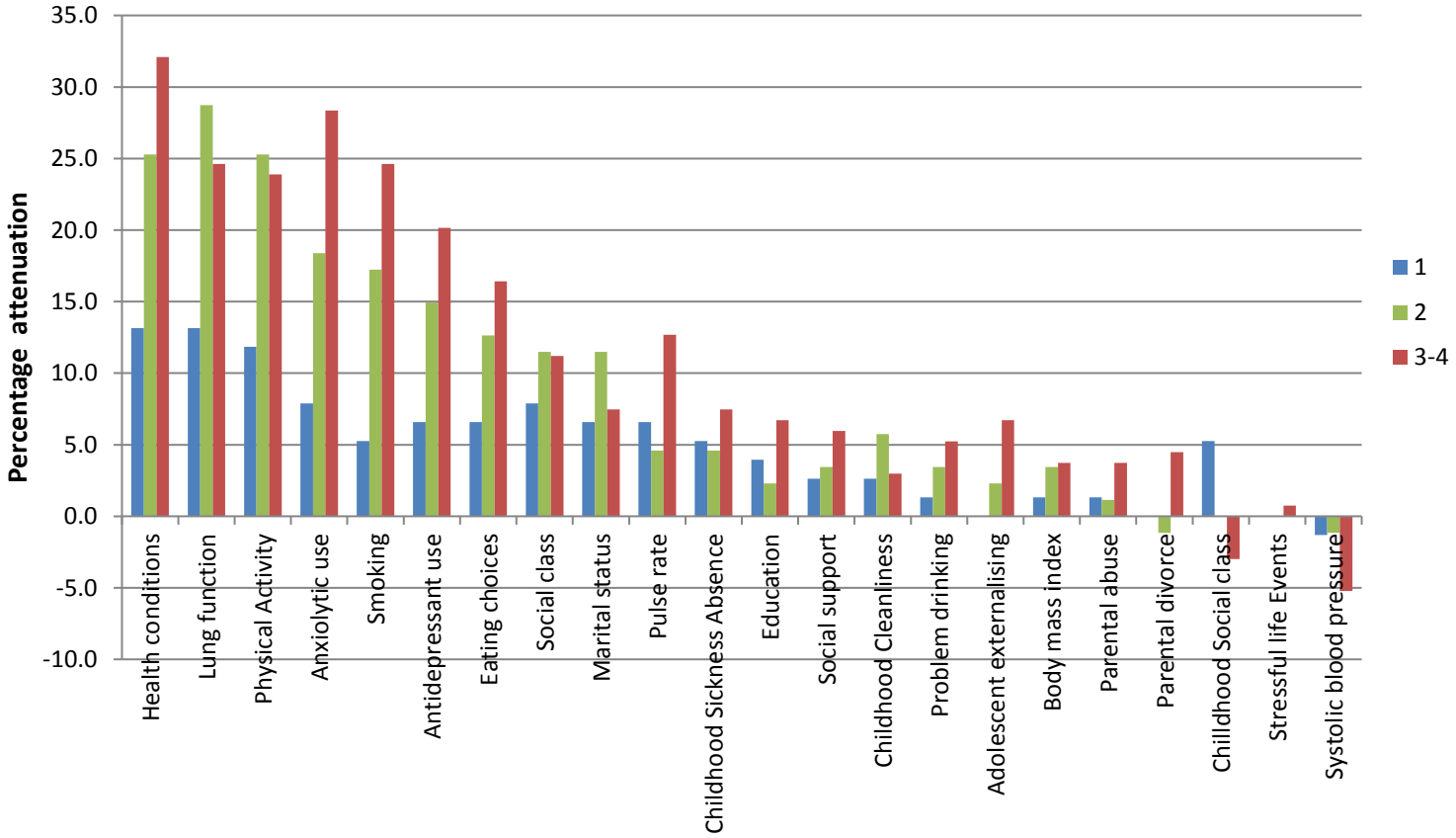

Figure 5.3.12.10 Percentage attenuation of the sex adjusted association between affective case history and mortality, by individual covariates (ordered by total absolute explanatory effect)

Table 5.3.12.11 shows that the sex adjusted associations between mortality and those who were a case 2 and 3-4 times were largely attenuated and no longer statistically significant after full adjustment for covariates (attenuated by 81.6% and 86.6%, respectively). In contrast, the association between those who were a case at a single time-point and mortality was only partially explained (attenuated by 39.5%), and continued to be associated with a 46% increased risk of mortality.

Table 5.3.12.11 Sex adjusted and fully adjusted hazard ratios for the association between affective case accumulation and mortality; based on 235 deaths and 15 imputations (n=3001)

	Mortality Hazard Ratio (95% CI)	
	Sex adjusted	**Fully adjusted**
Affective symptoms		
0	ref	ref
1	1.76 (1.29, 2.38)**	1.46 (1.06, 2.02)*
2	1.87 (1.18, 2.97)*	1.16 (0.72, 1.89)
3-4	2.34 (1.36, 4.04)*	1.18 (0.62, 2.25)
Sex		
Male	-	ref
Female	-	0.49 (0.34, 0.70)**
Adult social class		
Professional (I)	-	ref
Intermediate (II)	-	0.84 (0.47, 1.50)
Skilled, non-manual (III-NM)	-	0.74 (0.36, 1.55)
Skilled, manual (III-M)	-	0.95 (0.51, 1.77)
Partly skilled (IV)	-	1.11 (0.54, 2.28)
Unskilled (V)	-	0.96 (0.41, 2.25)
Education		
None	-	ref
O-level or equivalent	-	1.37 (0.96. 1.96)
A-level or equivalent	-	1.17 (0.76, 1.80)
Higher education	-	1.72 (0.91, 3.25)
Systolic blood pressure (mmHg)		
Per standard deviation	-	0.97 (0.82, 1.14)
Lung function (FEV_1)		
Per litre	-	0.65 (0.50, 0.85)**
Pulse rate (bpm)		
Per standard deviation	-	1.37 (1.20, 1.57)**
Body mass index (kg/m^2)		
Per standard deviation	-	1.09 (0.95, 1.25)
Health conditions		
0	-	ref
1	-	1.13 (0.79, 1.63)
2	-	1.66 (1.10, 2.53)*
3 or more	-	2.01 (1.18, 3.42)*
Smoking		
Never smoked	-	ref
Predominantly non-smoker	-	1.27 (0.84, 1.92)
Predominantly smoker	-	1.79 (1.17, 2.75)*
Lifetime smoker	-	2.16 (1.37, 3.40)**

Problem drinking		
No	-	ref
Yes	-	1.15 (0.79, 1.68)
Physical activity		
Inactive	-	ref
Least active	-	0.70 (0.50, 0.97)*
Most active	-	0.66 (0.43, 1.00)*
Eating Choices Index		
Per unit	-	0.96 (0.83, 1.11)
Antidepressant use		
No	-	ref
Yes	-	1.02 (0.62, 1.70)
Anxiolytic use		
No	-	ref
Yes	-	1.29 (0.81, 2.03)
Marital status		
Married or cohabiting	-	ref
Single	-	1.71 (1.03, 2.84)*
Divorced, widowed, separated	-	1.31 (0.88, 1.95)
Social support (friends)		
Always	-	ref
Often/sometimes/never	-	1.08 (0.77, 1.52)
Stressful life events		
0-5	-	ref
6-9	-	0.84 (0.60, 1.19)
10+	-	0.97 (0.59, 1.62)
Parental divorce		
No	-	ref
Yes	-	1.12 (0.66, 1.93)
Childhood cleanliness		
Amongst the best/average	-	ref
Amongst the worst	-	1.00 (0.46, 2.18)
Parental abuse		
No	-	ref
Yes	-	1.12 (0.64, 1.95)
Childhood social class		
Professional (I)	-	ref
Intermediate (II)	-	2.16 (0.91, 5.17)
Skilled, non-manual (III-NM)	-	2.15 (0.90, 5.15)
Skilled, manual (III-M)	-	1.82 (0.77, 4.29)
Partly skilled (IV)	-	2.50 (1.04, 6.00)*
Unskilled (V)	-	2.00 (0.76, 5.29)

Adolescent externalising		
Mild	-	ref
Moderate	-	0.87 (0.59, 1.31)
Severe	-	1.22 (0.74, 2.01)
Childhood sickness absence (weeks)		
0-4	-	ref
4-10	-	1.06 (0.77, 1.47)
10+	-	1.75 (1.18, 2.61)*

* $p < 0.05$

**$p < 0.001$

5.4 Discussion

5.4.1 Crude and sex adjusted associations between affective case accumulation and mortality

After adjustment for sex, there was an apparent dose-response relationship between the number of times a person was an affective case and mortality. The results build on previous studies among older persons which found a dose-response relationship between depressive symptom caseness and mortality (Geerlings et al., 2002; White et al., 2016) and cancer incidence (Penninx et al., 1998a). These findings suggest that each affective case has an independent influence on mortality risk and that the associations between affective symptoms and mortality observed at ages 43 and 53 (sections 4.3.3.4-5) were not driven solely by symptoms originating in adolescence.

Notably, the unadjusted Kapan Meier graph demonstrated a graded relationship but only in the first ten years of follow-up as the survival probability of those who were a case one or two times became increasingly similar in later years. It is possible that this was due to considerable heterogeneity among those who were a case one or two times with respect to the timing of symptoms (see table 5.3.6.2), which makes it difficult to interpret the results. For example, a single case could have been experienced in adolescence, or immediately prior to follow-up at age 53, so it is unlikely that these two sub-groups would exhibit the same relationship with mortality over time (the timing of affective caseness is investigated further in chapter 6).

Those who were a case 3-4 times appeared to have 2.3 times the risk of mortality compared to those who were never a case; however this association was driven largely by females, who accounted for approximately 82% of deaths within this category. Females were over two-and-a-half times as likely to be a case 3-4 times compared to males (table 5.3.5.1), which is consistent with a higher prevalence of CMD and depression in women across many different countries and cultures (Culbertson, 1997; National Centre for Social Research and Department of Health Sciences, 2009; Piccinelli and Wilkinson, 2000). There was no association between males who were a case 3-4 times and mortality, which is probably explained by low power within this category, as indicated by the very large confidence interval surrounding this estimate (HR=1.07, 95% CI: 0.27 to 4.26). Overall, there was no evidence of a sex interaction (joint Wald test, p=0.44), consistent with

analyses in chapter 4 and previous studies (Cole, 2007; White et al., 2016; Wulsin et al., 1999).

Sensitivity analyses

Moderate symptom accumulation and mortality

Sensitivity analysis demonstrated that there was no evidence of an association between moderate symptom accumulation and mortality. This suggests that there is a potential 'threshold effect' where only severe affective symptoms are associated with an increased risk of mortality, and that moderate symptoms in themselves are not a risk factor for mortality. The results also indicate that it is reasonable to use an affective case accumulation measure derived from binary 'case' variables which group no/mild and moderate symptoms into a single reference category.

Other studies have shown that moderate symptoms are associated with an increased mortality risk compared to those with no symptoms (Cuijpers and Smit, 2002; Henderson et al., 2011; White et al., 2015). However, these studies assessed affective symptoms at a single point in time, which means that the increased risk associated with moderate symptoms could be due to capturing those with a greater propensity for experiencing severe affective symptoms (Fergusson et al., 2005a; Hardeveld et al., 2013; Kessler et al., 2003).

Schizophrenia cases and externalising deaths

Excluding those with schizophrenia had relatively little impact on sex adjusted associations between affective symptoms and mortality, apart from a slight attenuation amongst those who were a case two times. This suggests that the observed associations between affective case accumulation and mortality were not confounded by schizophrenia, although there were only 17 cases of schizophrenia in the study sample.

Similarly, excluding externalising deaths (n=20) had almost no impact on the sex adjusted hazard ratios. Whilst externalising deaths account for a lower proportion of mortality at older ages (see table and figure 4.3.2.2), previous analyses also demonstrated that externalising deaths did not explain associations between affective symptoms and mortality earlier in the life course, as discussed earlier (see section 4.4). These results suggest that those who experienced an affective case were no more likely to die of externalising causes opposed to natural causes of death.

5.4.2 Multivariable associations between affective case accumulation and mortality

After full adjustment for all covariates, affective caseness at a single point in time was associated with a 46% increased risk of mortality, compared to those who were never a case. After full adjustment, the associations between mortality and those who were a case 2 or more times were largely explained and no longer statistically significant; although the hazard ratios remained slightly raised.

The association between affective case accumulation and mortality was most strongly explained by number of health conditions, lung function, and physical activity (> 10% attenuation across all levels of affective case accumulation). Among those who were a case 2-4 times, anxiolytic use, smoking, antidepressant use, diet, and adult social class also appeared to considerably attenuate associations with mortality (> 10% attenuation), which implies that there could be distinct explanatory pathways associated with those who experienced multiple affective caseness. These findings are consistent with previous community and population based studies, which found that physical illness/health conditions, physical activity and smoking most strongly attenuated associations between depressive symptoms and mortality (Mykletun et al., 2007; Penninx et al., 1998b; White et al., 2016, 2015). No previous study has tested whether lung function or diet act as explanatory factors.

Number of health conditions and lung function

It seems doubtful that a single episode of affective symptoms would lead to chronic health conditions, or poor lung function; therefore it could be speculated that these factors confound associations between single caseness and mortality. However, the timing of affective caseness is largely heterogeneous among those who were a case at a single point in time (see table 5.3.6.2) which makes it difficult to infer explanatory pathways. For example, an affective case occurring in adolescence is far more likely to be upstream of chronic health conditions compared to an affective case occurring in late-adulthood.

Among those who were a case at multiple time points, it is likely that chronic health conditions and lung function mediate associations with mortality. This is because there is a higher probability that affective symptoms originated earlier in the life course among those who experienced multiple affective caseness (see table 5.3.6.2). This is consistent with Houle (2013) who found that over a sixteen year period the relationship between depression and mortality was not explained by prior physical health, but that individuals

who experienced depression were more likely to go on and develop poor health and functional limitations (Houle, 2013).

Physical activity, smoking and diet

Across all levels of affective caseness, it is likely that physical activity predominantly mediates the association with mortality. Previous studies have shown that emerging depression is associated with individuals changing from being physically active to inactive (van Gool et al., 2003), and intervention and twin studies have found little evidence that physical activity leads to a reduction in affective symptoms (Chalder et al., 2012; De Moor et al., 2008; Mead et al., 2008). Notably, physical activity appeared to be a stronger explanatory factor compared to other health behaviours, such as smoking, diet, and problem drinking; this could imply that physical inactivity might also capture variability relating to poor physical health and functional limitations. It should also be noted however, that the results relating to eating choices should be interpreted with caution as over fifty percent of the data was imputed for this variable.

Among those with multiple affective caseness, it is likely that smoking has a reciprocal relationship with affective caseness. For instance, major depression has been shown to help maintain smoking behaviour (Glassman et al., 1990); conversely, nicotine dependence has been associated with an increased risk of developing depressive symptoms (Boden et al., 2010; Breslau et al., 1998). Explanatory mechanisms relating to eating choices are unclear due to limited studies of directionality between affective symptoms and diet (see section 1.5.4.4).

Over a person's lifetime however, it will become increasingly likely that physical inactivity, smoking, and poor dietary choices will contribute to the development of affective symptoms though their impact on physical health (Doll et al., 2004; Kant et al., 2009; Knoops et al., 2004; Paffenbarger Jr et al., 1993).

Psychotropic medication

Psychotropic mediation considerably attenuated associations among those who were an affective case 2-4 times, and potentially acts as a mediator. Colman et al., (2006) previously described psychotropic medication use in the NSHD and found that tricyclic medication accounted for 93% of antidepressant prescriptions between ages 26 and 43, but only 53% at age 53 following the introduction of SSRIs in the late 1980's. These figures suggest that the large majority of antidepressant prescriptions were for tricyclic antidepressants, which

have been shown to be particularly detrimental to health. For example, tricyclics have been associated with an increased risk of cardiovascular disease (Hamer et al., 2010b), hypertension (Licht et al., 2009) raised inflammation (Hamer et al., 2011a; Vogelzangs et al., 2012) and accelerated cancer progression (Marx, 1992; Sharpe et al., 2002; Sternbach, 2003).

Notably, previous studies have found that antidepressant medication did not explain associations between depression and mortality (Penninx et al., 1998b; White et al., 2016, 2015); however these studies did not distinguish between different types of antidepressants which could help explain this discrepancy. For example, White et al., (2016, 2015) collected data on medication use from 1998-2001, when tricyclic use was far less common.

No previous study investigating the relationship between affective symptoms and mortality has controlled for anxiolytic medication, which appeared to be an important explanatory factor. Whilst anxiolytic use has been strongly associated with an increased risk of death (Parsaik et al., 2015; Weich et al., 2014) there has been very little research as to why this might be.

Markedly, bivariate analyses showed that anxiolytic and antidepressant medication demonstrated a strong dose-response relationship with affective caseness. This acts as a crude internal validation of the main exposure, but also raises the question as to whether psychotropic medication captures severity and therefore represents an over-adjustment. Excluding psychotropic medication from the fully adjusted model slightly increased the hazard ratios for those who were an affective case twice (HR=1.49, 95% CI: 1.08, 2.05) and 3-4 times (HR=1.30, 95% CI: 0.71, 2.38).

Adult social class

It is likely the attenuating effect associated with adult social class can be explained by social gradients in smoking, diet, physical activity, and health (Ferrie et al., 2002; Marmot et al., 1991). Other studies examining the association between affective symptoms and mortality have found that adult social class had a relatively small explanatory effect (Mykletun et al., 2007; White et al., 2016, 2015).

Pulse rate

Pulse rate also appeared to attenuate the association between mortality and those who were an affective case two times. The effect of pulse rate was negligible when health behaviours were included in the model (not shown), although it is likely that pulse rate is on the causal pathway between health behaviours and mortality. No previous study appears to have adjusted for pulse rate (Barth et al., 2004; Cuijpers and Smit, 2002; Meijer et al., 2013; Rugulies, 2002; Wulsin et al., 1999).

Marital status

Marital status attenuated the association between mortality and those who were an affective case 3-4 times, but had again had little independent explanatory effect when other covariates were included in the model (results not shown). White et al., (2016) also demonstrated that 'living alone' had a relatively moderate attenuating effect on the age and sex adjusted association between depressive symptoms and mortality in British Civil Servants.

Notably, bivariate analyses demonstrated that those who experienced multiple affective caseness were no more likely to be single (never married), but were far more likely to be 'divorced, widowed or separated' (divorced or separated accounted for 88% of study members within this group). Other studies have also shown higher rates of psychiatric disorder among those who were previously married, compared to those who were never married (Williams et al., 1992). This suggests that strain caused by the transition out of marriage or co-habitation could explain part of the association between affective symptoms and marital status (Williams and Umberson, 2004). This is supported by Menaghan and Lieberman (1986) who found that those who were newly divorced experienced a substantial increase in depressive symptoms over the following four years, and that this increase appeared to be mediated by financial problems and loss of social support – particularity close confiding relationships. Whilst it could be proposed that affective symptoms place strain on existing relationships, longitudinal studies have found little evidence that psychological distress is a cause of divorce (Booth and Amato, 1991; Menaghan and Lieberman, 1986). This suggests that marital status is likely to be upstream on the causal pathway between affective caseness and mortality.

5.4.2.1 Factors with little or no explanatory role

Several covariates had no notable attenuating effect (<10% attenuation across all levels of affective caseness) whether included in sex adjusted or multivariable adjusted models; these included education, systolic blood pressure, BMI, problem drinking, perceived social support from friends, stressful life events, adverse childhood experiences (cleanliness of the child, parental divorce, and parental abuse), and other childhood factors (childhood social class, externalising behaviour, and childhood sickness absence).

Education

Educational attainment did not act as an explanatory factor, which is consistent with other studies (Houle, 2013; Mykletun et al., 2007). In contrast however, in the NSHD, severe adolescent emotional problems have been associated with over twice the odds of having no educational qualifications (Richards and Abbott, 2009). This could suggest that educational attainment might be a more important factor among those who experienced affective symptoms in adolescence, which is explored in the following chapter.

Systolic blood pressure

Adjustment for systolic blood pressure appeared to slightly strengthen associations between affective case accumulation and mortality, which can be attributed to the strong inverse association between systolic blood pressure affective case accumulation, as previously shown in the NSHD (Tikhonoff et al., 2014) and other cohort studies (Hildrum et al., 2011, 2008, 2007; Licht et al., 2009). Whilst Mykletun et al., (2007) found that adjusting for diastolic blood pressure had no notable effect on association between affective disorders and mortality, no previous study appears to have isolated the explanatory role of systolic blood pressure with respect to all-cause, or cardiovascular mortality (Barth et al., 2004; Meijer et al., 2011; Nicholson et al., 2006; Wulsin et al., 1999).

Alcohol consumption

Despite an established association between heavy alcohol consumption and affective symptoms (Boden and Fergusson, 2011; Fergusson et al., 2009) and mortality (Camacho et al., 1987; Markkula et al., 2012), problem drinking did not attenuate associations between affective case accumulation and mortality. Additional analyses (not shown) also found that alcohol consumption, obtained from five-day diet diary data, had no explanatory role.

These findings appear to be somewhat consistent with White et al., (2016), who demonstrated that 'alcohol consumption in the last year' moderately attenuated associations between chronic depressive symptoms and mortality in older persons; however White et al., (2016) found a strong dose-response relationship between zero alcohol consumption and depressive caseness, suggesting that the attenuating effect of alcohol consumption was driven by those who abstained from alcohol, opposed to heavy drinkers. This implies that other factors, such as poor physical health, could potentially account for the explanatory role associated with alcohol. Since health problems are more common at older ages, this could explain why alcohol did not appear to attenuate the relationship between affective case accumulation and mortality in the NSHD. Other studies have adjusted for alcohol but only within a larger group of covariates (Houle, 2013; Mykletun et al., 2007; Penninx et al., 1998b) so the unique contribution of alcohol is largely unknown.

ACE, stressful life events, and social support

Adverse childhood experience (ACE) variables (parental divorce, parental abuse, and childhood cleanliness) did not explain the association between affective case accumulation and mortality. This is consistent with Kelly et al., (2013) who found that in the 1958 British birth cohort, the relationship between ACE and mortality was not mediated by affective symptoms, and that affective symptoms retained an independent association with mortality, which could suggest that ACE and affective symptoms have different pathways to mortality. No other studies of affective symptoms and mortality appear to have examined the explanatory role of ACE.

It possible that the associations between ACE and mortality could be better explained by using measures of accumulated adversity. For instance, bivariate analyses demonstrated only weak evidence of an association between individual ACE and mortality, whilst previous studies have shown strong associations when using measures of multiple adversity (Brown et al., 2009; Geoffroy et al., 2014; Kelly-Irving et al., 2013). A summary measure of multiple adversities was not possible in these analyses due to a limited number of adversities recorded prior to the first measure of affective symptoms at age 13 (as discussed in section 3.6.6).

Stressful life events (SLE) demonstrated a very strong dose-response relationship with affective symptoms, consistent with studies showing that acute and chronic stressors

predict future depressive episodes (Colman et al., 2014; Hammen, 2005). However, there was no evidence that SLE attenuated associations between affective case accumulation and mortality. This is consistent with Houle (2013) who found that the association between depressive symptoms and mortality was not explained by recent stressful life events.

Other factors, such as social support, could buffer the impact of psychosocial stress on mortality (Cohen and Wills, 1985; Frasure-Smith et al., 2000), which could help explain why ACE and SLE demonstrate strong associations with affective symptoms, yet do little to explain the relationship between affective case accumulation and mortality. Nevertheless, perceived social support did not attenuate the association between affective case accumulation and mortality, and there was also no evidence that social support moderated the effect of affective symptoms on mortality. This is largely consistent with Houle et al., (2013) who found that the association between depressive symptoms and mortality was not explained by measures of formal or informal social integration.

It is possible that other measures of social support might better explain the relationship between affective symptoms and depression. For instance, the measure of social support used in this analysis captures instrumental support ("Do you think that you have friends or neighbours or relatives who would help if a problem or crisis came up?") but no study has controlled for perceived emotional support, which as previously mentioned, potentially mediates the association between divorce and psychological distress (Menaghan and Lieberman, 1986).

Sex specific relationships

Some covariates have also been shown to have a sex specific relationship with affective symptoms, although this does not appear to explain their lack of explanatory effect. In the NSHD, parental divorce has been shown to be a risk factor for depression in women, but not among men (Rodgers et al., 1997); likewise affective symptoms have been associated with a higher BMI among women, but a lower BMI among men (Gaysina et al., 2011). However, even among those who were a case 3-4 times (a category largely consisting of females) parental divorce and BMI had no attenuating effect. Furthermore, previous studies have shown that BMI does not attenuate associations between affective disorders and mortality (Mykletun et al., 2007).

Other childhood factors

Childhood social class did not explain associations between affective symptoms and mortality presumably because bivariate analysis demonstrated weak evidence of an association between affective case accumulation and childhood social class. This is consistent with other studies in the NSHD which found little relationship between childhood social class and affective disorders in adulthood (Rodgers, 1990).

Childhood sickness absence and adolescent externalising demonstrated associations with both affective case accumulation and mortality; but only very slightly attenuated associations between those who were an affective case 3-4 times and mortality. This suggests that externalising behaviour does not confound associations between affective case accumulation and mortality, and that childhood sickness and affective symptoms may have independent pathways to mortality. No other studies investigating the association between affective symptoms and mortality have adjusted for childhood social class, adolescent externalising behaviour, or childhood sickness.

Limitations

Low power is a key limitation which meant that there was insufficient data to establish the risk of mortality among males who experienced an affective case 3-4 times. Likewise, the results relating to moderate symptoms should be interpreted with caution due to the restricted sample size in this analysis.

The validity of the affective case accumulation variable is based on the assumption that measures of affective caseness across ages 13-15, 36, 43, and 53 measure the same construct. Whilst each measure is different with respect to the mode of data collection (teacher-rated, self-report, and clinical interview) in addition to the window of assessment ranging from one month to one year; there is strong reason to believe that each measure captures a comparable construct, that is, symptoms of anxiety and depression (see section 3.4.9).

As mentioned previously, it is likely that the explanatory pathways between affective caseness and mortality are different depending on the timing of an affective case. This means that the attenuating role of each covariate could vary, particularly among those who were a case at a single point in time. For example, it is possible that ACE could strongly explain associations between adolescent affective caseness and mortality, but have no

explanatory role with regard to the relationship between affective caseness at age 53 and mortality. The timing of affective symptoms is explored further in the following chapter.

The attenuating effect of each covariate is also likely to be modified by cause of death; for example, BMI, pulse rate, smoking and stressful life events might play a stronger role with respect to cardiovascular mortality. However, due a low number of deaths, it was not possible to conduct multivariable analyses by cause-specific mortality. Sex adjusted associations between affective symptoms and cause-specific mortality are examined in chapter 7.

5.5 Summary

Sex adjusted analyses

After adjustment for sex, there was evidence of an accumulation effect where the risk of mortality increased as affective caseness increased. Those who were a case 3-4 times had over twice the risk of mortality compared to those who were never a case, although this association was largely driven by females. Inadequate power meant that it was not possible to estimate mortality risk among males who were a case 3-4 times.

Sensitivity analyses suggested that schizophrenia and externalising deaths did not explain sex adjusted associations between affective case accumulation and mortality, consistent with findings from chapter 4.

There was no evidence that moderate affective symptom accumulation increased the risk of mortality, which suggests that severe affective symptoms were driving associations between affective symptoms and mortality.

Multivariable analyses

After full adjustment, those who were a case at a single point in time had a 46% increased risk of mortality compared to those who were never a case, while the association between mortality and those who were an affective case 2 and 3-4 times was largely attenuated and no longer statistically significant.

The strongest explanatory factors across all levels of affective case accumulation were number of health conditions, lung function, and physical activity. Among those who were a

case 2-4 times, smoking, diet, anxiolytic use, and antidepressant use also appeared to considerably attenuate associations with mortality. This suggests there could be distinct explanatory pathways associated with multiple affective caseness.

More moderate attenuation was observed with respect to adult social class, pulse rate, and marital status. These variables had little or no independent explanatory effect once other covariates were included in the model, although there is evidence to suggest that pulse rate and marital status ('divorce, separation and widowhood') are on the causal pathway.

There was little evidence that education, systolic blood pressure, BMI, problem drinking, perceived social support from friends, stressful life events, adverse childhood experiences (cleanliness of the child, parental divorce, and parental abuse), and other childhood factors (childhood social class, externalising behaviour, and childhood sickness absence) had an explanatory role.

Among those who were a case at a single point in time, it is likely that health conditions, and lung function, confound associations with mortality; however, these factors are perhaps more likely to mediate associations with respect to multiple affective caseness. Physical activity is likely to act as a mediator, smoking as both a mediator and confounder, whilst the explanatory pathways relating to diet remain unclear. It is probable that psychotropic medication mediates associations between affective case accumulation and mortality, but may also reflect an over-adjustment.

Whether each covariate is a potential mediator or confounder is largely dependent on its timing relative to affective caseness. The next chapter will examine the role of affective case history, which should help further elucidate potential explanatory pathways – particularly with regard to those who were a case at a single point in time.

6. LIFETIME AFFECTIVE CASE HISTORY AND MORTALITY

6.1 Chapter overview

This chapter presents the results of analyses relating primarily to objective 2: To investigate the association between affective symptoms and mortality with respect to affective case history (never, adolescent only, new-onset, intermittent, chronic); and objective 3.1-7: To investigate to what extent the relationship between lifetime affective history and mortality can be explained by the following factors: physical health status, health behaviours, psychotropic medication use, social networks, stressful life events, and adverse childhood experiences.

The following hypotheses were tested:

2.2 Adult new-onset symptoms will predict mortality, indicative of reverse causality with poor physical health.

3.0 Physical health status, health behaviours, psychotropic medication use, social networks, stressful life events, and adverse childhood experiences will all partially explain the association between lifetime affective case history and mortality

This chapter largely repeats the analyses presented in chapter 5, but with respect to patterns of affective case history rather than accumulation. Descriptives characteristics of affective case history are presented, followed by crude and sex adjusted associations between affective case history and mortality, including sensitivity analyses. The sex-adjusted relationship between affective case history and mortality is also shown by length of follow-up.

The results of bivariate and sex adjusted associations between all covariates and affective case history are then presented, followed by multivariable analyses where the explanatory role of each covariate is demonstrated with respect to the relationship between affective case history and mortality. Finally, the results are discussed with a particular focus on the timing of symptoms.

The sex adjusted associations between affective case history and mortality were similar for the imputed and non-imputed datasets (see Appendix K for non-imputed results); therefore only the results of the imputed analyses are presented.

6.2 Methods

6.2.1 Exposure variable

The main exposure variable used in this chapter is affective case history, which consists of five profiles (never, adolescent only, new-onset, intermittent, chronic) and was derived from the affective 'case' variables at ages 13-15, 36, 43, and 53 (described in detail in sections 3.4.1-8). An affective case refers to those who experienced severe affective symptoms. 'Never' and 'chronic' caseness are identical to those who were a case 0 and 3-4 times, respectively.

6.2.2 Outcome variable

The outcome variable is all-cause mortality (as described previously in section 3.5), with follow-up from age 53 onwards.

6.2.3 Analytical strategy

The association between affective case history and mortality was assessed using imputed data in an identical manner to that described previously for affective case accumulation (see section 5.2.4); however, sensitivity analyses also included a 3-year wash-out period to test for reverse causality with poor physical health, specifically for those experiencing 'new' affective caseness at age 53. The strength of crude and sex adjusted associations between affective case history and all other exposures were estimated by a Wald test using multinomial logistic regression.

Exploratory analyses were conducted using piece-wise Cox regression to examine the relationship between affective case history and mortality in the first four years of follow-up, compared to later years. This was because 'new' caseness was associated with a sharp drop in survival probability in the first four years of follow-up (demonstrated in figure 6.3.3).

The sex-adjusted relationship between affective case history and mortality was also assessed in the original (non-imputed) data in order to compare the hazard ratios obtained from the original and imputed data.

6.3 Results: Crude and sex adjusted associations between affective case accumulation and mortality from age 53 onwards

6.3.1 Participants

The study sample is identical to that used in the previous chapter (see section and figure 5.3.1)

6.3.2 Descriptive characteristics of mortality

Identical to the previous chapter, mortality follow-up time was from age 53 (1999) to mortality, or censored due to emigration or end October 2014. Mean follow-up was 14.4 years (range 0.08-15.0), during which there were 235 deaths (102 male and 133 female). See Appendix L for a comparison between non-imputed and imputed mortality descriptives by affective case history.

6.3.3 Descriptive characteristics of affective case history comparing the original and imputed data

Table 6.3.3 shows that the imputed descriptives for affective case history are similar to the original dataset; the imputed sample has a slightly higher level of overall caseness, but a lower level of those with new affective caseness.

The imputed data show that males and females had broadly comparable levels of adolescent-only and new caseness; however females were far more likely than males to experience intermittent or chronic caseness.

Table 6.3.3 Affective case history descriptives for original (n=2066) and imputed data (n=3001)

	Original	Imputed		
	All	All	Males	Females
	%	%	%	%
Affective case history[a]				
Never	57.8	56.3	64.5	48.3
Adolescent only	8.0	8.8	8.7	9.0
New	8.3	7.4	6.4	8.4
Intermittent	21.6	22.8	17.8	27.8
Chronic	4.3	4.6	2.6	6.6

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); chronic = case 3-4 times.

6.3.4 Power analyses for the association between affective case history and mortality

Table 6.3.4 Power for affective case history based on a 5.2% risk of all-cause mortality among those who were never a case, and alpha 0.05 (non-imputed data, n=2066)

	Power (%)			
	Adolescent only (n=165)	**New (n=172)**	**Intermittent (n=446)**	**Chronic (n=88)**
Hazard ratio				
1.2	7.9	8.0	12.8	5.9
1.4	19.6	20.1	36.3	13.1
1.6	37.3	38.4	65.5	23.8
1.8	57.9	59.4	86.9	40.0
2.0	76.2	77.6	96.6	53.8
2.5	97.5	97.9	100.0	86.0

Table 6.3.4 shows that there was adequate power to detect hazard ratios greater than 1.8 for those with intermittent caseness. For those with adolescent-only, new, and chronic caseness, there was reasonable power to detect hazard ratios in the region of 2.0-2.5 only. Across all levels of affective case accumulation, there was a high chance of type II error for detecting hazard ratios less than 1.4.

6.3.5 Crude and sex adjusted associations between affective case history and mortality

The Kaplan Meier chart (figure 6.3.5) shows that at the end of follow-up, study members with chronic caseness had the lowest survival probability; those with new, adolescent only, or intermittent caseness had relatively similar survival probabilities, whilst those who were never a case had the highest survival probability.

Notably, in the first four years of follow-up, new caseness appears to have the lowest survival probability before tailing off; although the proportional hazards assumption was not violated (p=0.18 for new caseness). In contrast, survival curves for never, intermittent, and chronic caseness all appear to demonstrate a relatively consistent decline in survival probability.

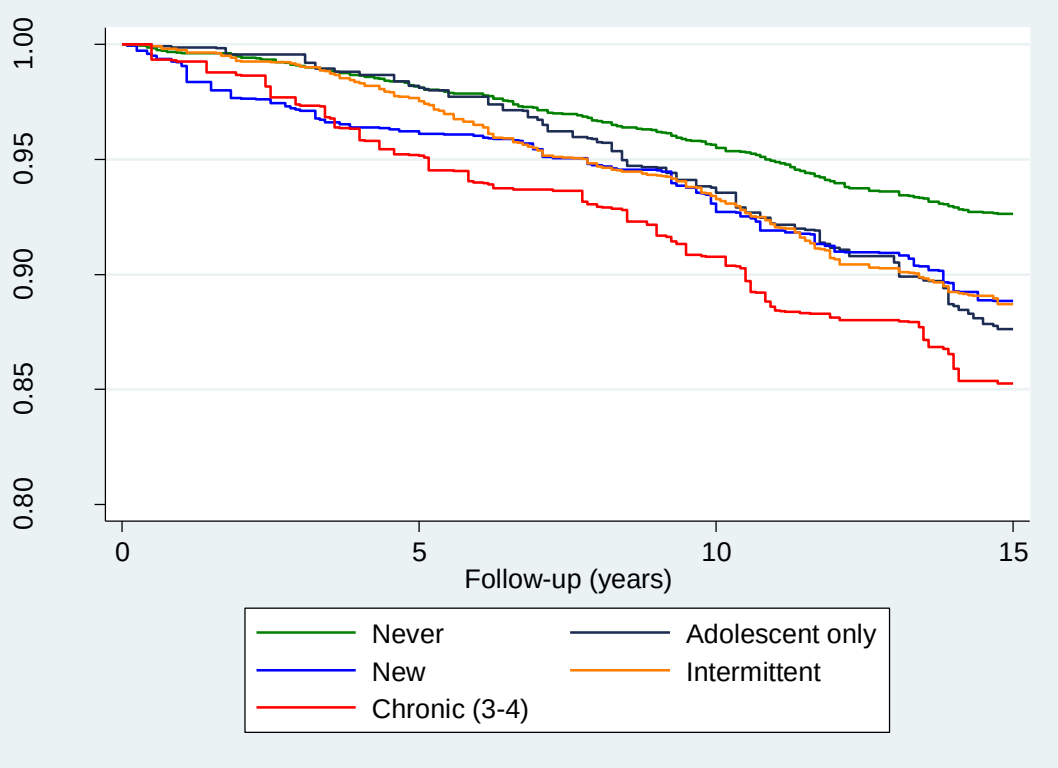

Figure 6.3.5 Unadjusted Kaplan-Meier survival curves for all-cause mortality by affective case history; based on 235 deaths, n=3001, and 15 imputations

Table 6.3.5.1 shows that after adjustment for sex, adolescent only, intermittent, and chronic caseness were all associated with an increased risk of mortality, whereby chronic caseness appears to be the strongest risk factor. The hazard ratio for new caseness is also raised; however this association was not statistically significant.

All sex interaction terms were not statistically significant ($p \geq 0.2$) as indicated by the largely overlapping confidence intervals.

Table 6.3.5.1 Sex adjusted hazard ratios for the association between affective case history and mortality; based on 235 deaths, n=3001 and 15 imputations

	Hazard ratio (95% CI)		
	Sex adjusted	Males (n=1492)	Females (n=1509)
Affective case history			
Never	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.53 (0.81-2.86)	2.69 (1.44-5.03)*
New	1.67 (0.96-2.89)	1.60 (0.77-3.31)	1.78 (0.80-3.92)
Intermittent	1.74 (1.26-2.40)*	1.98 (1.32-2.98)*	1.54 (0.91-2.61)
Chronic	2.34 (1.36-4.03)*	1.07 (0.27-4.26)	3.19 (1.69-6.04)**

* $p < 0.05$

**$p < 0.001$

Table 6.3.5.2 shows that after adjustment for sex, excluding schizophrenia symptoms and excluding externalising deaths had very little effect on the hazard ratios. However, the inclusion of a 3 year wash-out period appears to attenuate the hazard ratios for new and chronic caseness, whilst strengthen the association with respect to adolescent only and intermittent caseness.

Table 6.3.5.2 Sex adjusted hazard ratios for the association between lifetime affective caseness and mortality, excluding schizophrenia cases, excluding externalising deaths, and including a 3-year wash-out

	Hazard ratio (95% CI)			
	Sex adjusted (n=3001, 235 deaths)	**+ excluding schizophrenia** (n=2984, 231 deaths)	**+ excluding externalising** deaths (n=2981, 215 deaths)	**+ 3 year wash-out** (n=2959, 205 deaths)
Affective case history				
Never	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.94 (1.25, 3.03)*	2.04 (1.30, 3.20)*	2.23 (1.41, 3.53)*
New	1.67 (0.96-2.89)	1.67 (0.96, 2.89)	1.63 (0.93, 2.88)	1.34 (0.72, 2.47)
intermittent	1.74 (1.26-2.40)*	1.69 (1.22, 2.34)	1.69 (1.21, 2.37)*	1.89 (1.35, 2.65)**
Chronic	2.34 (1.36-4.03)*	2.30 (1.31, 4.02)*	2.32 (1.32, 4.09)*	2.16 (1.18, 3.96)*

* $p < 0.05$

**$p < 0.001$

Consistent with the aforementioned results of the three year wash-out period, the Kaplan Meier survival curves demonstrated that 'new' caseness was associated with a sharp drop in survival probability in the first four years of follow-up (figure 6.3.3), as noted previously. In order to investigate this in more detail, exploratory analyses were conducted to examine the role of new caseness in the first four years of follow-up compared to the last eleven years.

Table 6.3.3.3 shows that after adjustment for sex, there was a strong association between new affective symptoms and mortality in the first four-years of follow-up, but no evidence of an association in later years.

Adolescent and intermittent caseness were not associated with mortality in the first four years of follow-up, although this is probably due to the very low number of deaths during this period – as reflected by the wide confidence intervals.

Table 6.3.5.3 Sex adjusted hazard ratios for the association between affective case history and mortality by follow-up time; based on 15 imputations

	Hazard ratio (95% CI)	
	≤ 4 years (n=3001, 42 deaths)	> 4 years (n=2947, 193 deaths)
Affective case history		
Never	ref	ref
Adolescent only	1.17 (0.32-4.29)	2.15 (1.33-3.46)*
New	3.49 (1.27-9.60)*	1.26 (0.67-2.37)
Intermittent	1.24 (0.62-2.94)	1.85 (1.31-2.62)**
Chronic	3.26 (1.10-9.62)*	2.11 (1.13-3.97)*

* $p < 0.05$

**$p < 0.001$

6.3.6 Crude and sex adjusted associations between affective case history and all exposures

Table 6.3.6 shows that there were statistically strong ($p<0.001$) crude and sex adjusted associations between affective case history and sex, lung function, number of self-reported health conditions, smoking, problem drinking, physical activity, eating choices, antidepressant use, anxiolytic use, marital status, social support, stressful life events, parental divorce, and parental abuse. More moderate associations ($p<0.05$) were observed with regard to adult social class, education, systolic blood pressure, adolescent externalising and childhood cleanliness. There was less evidence of an association with regard to pulse rate, BMI, childhood cleanliness, and childhood social class.

Adjustment for sex appeared to slightly weaken the association between affective case history and adult social class, education and systolic blood pressure; however associations were strengthened with respect to eating choices and childhood cleanliness. Adjustment for sex did not notably alter associations between affective case history and all other covariates.

Females were far more likely than males to experience intermittent or chronic caseness and least likely to have never have been a case. Study members who were never a case appeared more likely to belong to a professional or intermediate adult social class compared to other types of affective case history. Those who experienced chronic caseness and adolescent only caseness appeared most likely to have no educational qualifications, and least likely to have completed higher education.

Systolic blood pressure, lung function, and physical activity levels were lowest among chronic caseness and highest among those who were never a case, whilst number of self-reported health conditions were highest among those with chronic caseness and lowest among those who were never a case. Although the not statistically significant, pulse rate appeared highest among those with adolescent only caseness, closely followed by chronic caseness, and lowest among those who were a new case, whilst BMI was highest among those with chronic and new caseness, and lowest among those with adolescent-only caseness.

Dietary scores were poorest among those with chronic caseness, but highest among those with new caseness. Smoking prevalence, problem drinking, anti-depressant and anxiolytic use appeared highest among chronic caseness, and lowest among adolescent only

caseness; problem drinking was particularly low among study members who were a case in adolescence only.

Those with adolescent only caseness were also most likely to be single, whilst those with intermittent or chronic caseness were most likely to be divorced, widowed or separated, compared with all other affective case histories. Perceived social support appeared to be highest among those who were never a case, and lowest among those with chronic caseness. Number of stressful life events was highest for those with chronic caseness, and lowest among those who were a case in adolescence only.

Parental divorce and parental abuse appeared particularly high among study members who experienced chronic caseness compared to all other types of affective case history. Cleanliness of the child appeared to be slightly poorer among those with chronic and intermittent affective caseness, and best among those who were never a case.

Study members with adolescent only and new caseness appeared more likely to have a lower childhood social class compared to all other affective case histories. Severe adolescent externalising was highest among those with chronic caseness relative to all other affective case histories, whilst childhood sickness absence (four or more weeks) was highest among those with adolescent only caseness, and lowest among those who were never a case.

Comparison with affective case accumulation

If the relationship between affective caseness and mortality was determined by accumulation only, it might be expected that adolescent-only and new affective caseness would demonstrate a similar pattern of association to those who were a case at a single time-point (see table 5.3.10). However, compared to all other types of affective case history (including 'never'), study members with adolescent-only caseness had the lowest levels of smoking, problem drinking, anxiolytic use, stressful life events and adolescent externalising, yet the highest levels of childhood sickness absence, and the highest likelihood of being single. In contrast, those with new caseness followed a similar pattern to those who were a case at a single time-point, with the exception of having a healthier dietary score, and reporting a higher number of stressful life events.

Intermittent caseness appeared to follow a pattern of association with the exposure variables consistent with those who were a case at one or two time-points (see Appendix E for cross tabulation of affective case accumulation an affective case history).

Table 6.3.6 Crude and sex adjusted associations between affective case history[a] and all exposures (n=3001)

	%						
Exposure	**Never**	**Adolescent only**	**New**	**Intermittent**	**Chronic**	**P[b]**	**p[c]**
Sex							
Male	56.9	48.9	43.1	38.8	28.1	<0.001	N/A
Female	43.1	51.1	56.9	61.2	71.9		
Social class (adult)							
Professional (I)	11.3	6.5	10.6	9.0	9.3	0.003	0.02
Intermediate (II)	41.9	31.9	33.8	36.4	33.4		
Skilled, non-manual (III-NM)	10.6	16.2	14.4	13.9	11.3		
Skilled, manual (III-M)	25.1	31.7	26.0	24.4	25.6		
Partly skilled (IV)	8.3	9.4	9.0	11.8	13.7		
Unskilled (V)	2.8	4.3	6.2	4.5	6.7		
Education							
None	34.0	44.9	36.9	37.9	45.9	0.008	0.04
O-level or equivalent	28.0	28.0	29.9	28.7	31.1		
A-level or equivalent	27.2	22.5	25.1	24.6	15.7		
Higher education	10.9	4.6	8.1	8.8	7.2		
Systolic blood pressure (mmHg)							
Mean (SD)	137.4 (19.8)	136.7 (19.4)	133.9 (20.4)	134.8 (20.1)	130.6 (18.3)	0.01	0.32
Lung function (FEV_1)							
Mean (SD)	2.81 (0.70)	2.61 (0.74)	2.66 (0.74)	2.54 (0.70)	2.36 (0.64)	<0.001	<0.001
Pulse rate (bpm)							
Mean (SD)	68.0 (11.4)	69.5 (12.3)	67.9 (12.1)	68.4 (11.4)	69.4 (12.5)	0.31	0.23

Body mass index (kg/m2)							
Mean (SD)	27.4 (4.5)	27.1 (4.9)	28.0 (5.4)	27.6 (5.1)	28.1 (5.4)	0.16	0.20
Health conditions							
0	54.4	49.9	40.0	39.3	26.2	<0.001	<0.001
1	28.6	31.3	32.2	33.6	30.1		
2	11.4	12.4	19.0	16.4	26.3		
3 or more	5.5	6.5	8.9	10.6	17.4		
Smoking							
Never smoked	29.5	38.4	25.3	24.5	21.2	<0.001	<0.001
Predominantly non-smoker	35.1	37.8	31.3	32.1	28.8		
Predominantly smoker	20.7	14.8	27.8	23.6	26.1		
Lifetime smoker	14.7	9.1	15.6	19.8	24.0		
Problem drinking							
No	89.2	95.3	90.0	85.2	82.9	<0.001	<0.001
Yes	10.8	4.7	10.0	14.8	17.1		
Physical activity							
Inactive	16.2	24.1	21.1	21.9	29.8	<0.001	<0.001
Least active	46.4	50.9	44.8	45.6	50.4		
Most active	37.4	25.0	34.1	32.5	19.7		
Eating choices (ECI)							
Mean (SD)	8.61 (1.41)	8.48 (1.50)	8.68 (1.42)	8.47 (1.41)	8.37 (1.57)	0.15	0.004
Antidepressant use							
No	95.5	94.4	85.8	81.7	62.2	<0.001	<0.001
Yes	4.5	5.6	14.2	18.4	37.8		
Anxiolytic use							
No	95.8	95.9	92.5	83.9	67.5	<0.001	<0.001
Yes	4.2	4.1	7.6	16.1	32.5		

Marital status							
Married or cohabiting	81.5	77.3	79.2	73.6	71.3	<0.001	<0.001
Single	4.6	10.7	6.3	5.3	5.2		
Divorced, widowed, separated	13.9	12.0	14.5	21.1	23.5		
Social support (friends)							
Always	85.0	79.5	78.2	79.6	64.3	<0.001	<0.001
Often, sometimes, or never	15.0	20.5	21.8	20.4	35.7		
Stressful Life events							
0-5	63.5	71.8	40.6	40.6	25.2	<0.001	<0.001
6-9	30.2	23.6	42.3	40.3	39.9		
10+	6.4	4.7	17.2	19.2	34.9		
Parental divorce							
No	95.4	95.7	94.2	95.0	85.0	<0.001	<0.001
Yes	4.6	4.3	5.8	5.0	15.0		
Cleanliness of child							
Amongst the best / average	98.0	97.0	97.7	96.2	96.2	0.28	0.13
Amongst the worst	2.0	3.1	2.3	3.8	3.8		
Parental abuse							
No	95.5	93.7	95.0	91.3	81.6	<0.001	<0.001
Yes	4.5	6.4	5.0	8.7	18.4		
Social class (childhood)							
Professional (I)	6.6	3.2	3.0	6.8	10.2	0.18	0.18
Intermediate (II)	20.3	16.2	19.8	19.9	14.3		
Skilled, non-manual (III-NM)	16.2	16.5	19.7	15.3	18.7		
Skilled, manual (III-M)	33.3	33.0	27.4	33.5	34.2		

Partly skilled (IV)	18.2	23.6	21.9	17.7	18.3		
Unskilled (V)	5.4	7.5	8.1	6.8	4.4		
Adolescent externalising							
Mild	77.0	83.0	74.5	75.5	68.7	0.03	0.01
Moderate	17.3	12.8	19.5	16.8	18.1		
Severe	5.7	4.2	6.1	7.7	13.3		
Childhood sickness absence (weeks)							
0-4	54.8	45.4	52.1	52.9	48.9	0.02	0.02
4-10	35.8	37.1	35.2	36.6	33.9		
10+	9.4	17.6	12.8	10.6	17.2		

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); chronic = case 3-4 times.

b: P values obtained from Wald test/joint Wald test using multinomial logistic regression (unadjusted)

c: P values obtained from Wald test/joint Wald test using multinomial logistic regression (sex adjusted)

6.3.7 Multivariable adjusted associations between affective case history and mortality

Tables 6.3.7.1-9 shows the impact of each individual covariate and each group of covariates on the sex adjusted association between affective case history and mortality.

Table 6.3.7.1 shows that the sex adjusted hazard ratios for adolescent only, and chronic caseness were slightly attenuated by adjustment for adult social class, and to a lesser extent education; although the associations remained statistically significant. Adjustment for all socio-economic variables had little impact on the hazard ratios for new or intermittent caseness.

Table 6.3.7.2 indicates that the sex adjusted hazard ratios for affective case history were all partially attenuated after adjustment for all health status variables, whereby the association between chronic caseness and mortality was no longer statistically significant. The association between mortality chronic caseness was most strongly attenuated by lung function, number of self-reported health conditions and pulse rate. Similarly, intermittent caseness was most strongly attenuated by lung function and number of self-reported health conditions. Notably, the sex adjusted hazard ratio for new caseness was only attenuated by number of self-reported health conditions; whilst the hazard ratio for adolescent only caseness was only attenuated by lung function, and to a lesser extent pulse rate.

Table 6.3.7.3 shows that the sex adjusted hazard ratios for chronic and intermittent caseness were partially attenuated after adjustment for all health behaviour variables, although the associations remained statistically significant. The variables which most strongly accounted for the attenuation were smoking and physical activity, and to a lesser extent eating choices. Similarly, the hazard ratio for new caseness was partially attenuated by smoking, and marginally attenuated by physical activity. In contrast, the association between adolescent-only caseness and mortality was negatively confounded by smoking (i.e. smoking appeared to operate a suppressor effect), but also partially attenuated by physical activity; consequently, the health behaviour variables appeared to have an overall negligible influence on adolescent-only caseness.

Table 6.3.7.4 shows that the sex adjusted hazard ratios for intermittent and chronic caseness were partially attenuated after adjustment for psychotropic medication variables, although the associations remained statistically significant. The associations for adolescent-

only and new caseness were largely unaffected by adjustment for psychotropic medication, which reflects the relatively low use of psychotropic medication in these groups (see bivariate Table 6.3.4).

Table 6.3.7.5 shows that the sex adjusted hazard ratios for adolescent only, intermittent and chronic caseness were slightly attenuated after adjustment for social network variables, although the associations remained statistically significant. The attenuation was most strongly accounted for by marital status. The association between new caseness and mortality was relatively unaffected after adjustment for social network variables.

There was no evidence of an interaction between affective case history and social support (joint Wald test, p=0.22), which was conducted to test whether social support buffered the effect of affective symptoms on mortality.

Table 6.3.7.6 shows that the sex adjusted hazard ratios for affective case history were largely unaffected by adjustment for stressful life events, which included death of a loved one, illness, injury, moving house, burglary, divorce or separation, and crises with regard to employment, family, and children.

Table 6.3.7.7 shows that the sex adjusted hazard ratios for affective case history were relatively unaffected by adjustment for adverse childhood experience variables. There was very slight attenuation of the hazard ratios among those with chronic caseness, which was accounted for by parental abuse and parental divorce.

Table 6.3.7.8 shows that the sex adjusted hazard ratios for affective case history were largely unaffected by adjustment for other childhood factors. The hazard ratio for adolescent only caseness was slightly attenuated by childhood social class and childhood sickness absence, whilst the hazard ratio for chronic caseness was slightly attenuated by adolescent externalising and childhood sickness absence.

Table 6.3.7.1 Hazard ratios for the association between affective case history and mortality, adjusted for socio-economic variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)			
	Sex adjusted	Sex + social class	Sex + education	All
Affective history[a]				
Never	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.87 (1.20, 2.90)*	1.90 (1.23, 2.96)*	1.89 (1.21, 2.94)*
New	1.67 (0.96-2.89)	1.61 (0.93, 2.79)	1.64 (0.95, 2.85)	1.61 (0.93, 2.79)
Intermittent	1.74 (1.26-2.40)*	1.68 (1.22, 2.32)*	1.73 (1.25, 2.38)*	1.70 (1.24, 3.73)*
Chronic	2.34 (1.36-4.03)*	2.18 (1.26, 3.78)*	2.25 (1.30, 3.89)*	2.16 (1.24, 3.73)*

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.2 Hazard ratios for the association between affective case history and mortality, adjusted for health status variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)						
	Sex adjusted	Sex + Systolic blood pressure	Sex + Lung function	Sex + Pulse rate	Sex + Body mass index	Sex + health conditions	All
Affective history[a]							
Never	ref	ref	ref	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.98 (1.28, 3.07)*	1.79 (1.15, 2.78)*	1.87 (1.21, 2.91)*	1.99 (1.29, 3.09)*	1.93 (1.24, 3.00)*	1.72 (1.11, 2.69)*
New	1.67 (0.96-2.89)	1.70 (0.98, 2.95)	1.65 (0.95, 2.88)	1.64 (0.95, 2.84)	1.64 (0.95, 2.85)	1.54 (0.89, 2.67)	1.51 (0.87, 2.62)
Intermittent	1.74 (1.26-2.40)*	1.76 (1.27, 2.42)*	1.60 (1.15, 2.21)*	1.71 (1.24, 2.37)*	1.72 (1.25, 2.37)*	1.58 (1.14, 2.18)*	1.50 (1.08, 2.09)*
Chronic	2.34 (1.36-4.03)*	2.40 (1.39, 4.14)*	2.01 (1.15, 3.48)*	2.17 (1.26, 3.74)*	2.29 (1.32, 3.95)	1.90 (1.09, 3.32)*	1.63 (0.92, 2.87)

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.3 Hazard ratios for the association between affective case history and mortality, adjusted for health behaviour variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)					
	Sex adjusted	Sex + eating choices	Sex + lifetime smoking	Sex + problem drinking	Sex + physical activity	All
Affective history[a]						
Never	ref	ref	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.90 (1.23, 2.94)*	2.21 (1.42, 3.45)**	2.02 (1.30, 3.13)*	1.79 (1.15, 2.78)*	2.05 (1.31, 3.20)*
New	1.67 (0.96-2.89)	1.67 (0.96, 2.91)	1.57 (0.90, 2.74)	1.67 (0.96, 2.89)	1.60 (0.92, 2.78)	1.56 (0.89, 2.72)
Intermittent	1.74 (1.26-2.40)*	1.65 (1.20, 2.28)*	1.59 (1.15, 2.20)*	1.70 (1.23, 2.35)*	1.63 (1.18, 2.26)*	1.51 (1.09, 2.09)*
Chronic	2.34 (1.36-4.03)*	2.11 (1.21, 3.69)	1.99 (1.15, 3.45)*	2.26 (1.31, 3.91)*	2.02 (1.17, 3.51)*	1.75 (1.00, 3.05)*

* $p < 0.05$

**$p < 0.001$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.4 Hazard ratios for the association between affective case history and mortality, adjusted for psychotropic medication variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)			
	Sex adjusted	Sex + anxiolytic use	Sex + antidepressant use	All
Affective history[a]				
Never	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.98 (1.27, 3.07)*	1.97 (1.27, 3.04)*	1.97 (1.27, 3.06)*
New	1.67 (0.96-2.89)	1.63 (0.94, 2.83)	1.60 (0.93, 2.77)	1.60 (0.92, 2.77)
Intermittent	1.74 (1.26-2.40)*	1.60 (1.15, 2.23)*	1.64 (1.18, 2.28)*	1.56 (1.12, 2.18)*
Chronic	2.34 (1.36-4.03)*	1.93 (1.09, 3.43)*	2.05 (1.15, 3.66)*	1.83 (1.01, 3.30)*

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.5 Hazard ratios for the association between affective case history and mortality, adjusted for social network variables; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)			
	Model A: Sex adjusted	Sex + marital status	Sex + social support	All
Affective History[a]				
Never	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.87 (1.20, 2.92)*	1.96 (1.26, 3.04)*	1.86 (1.19, 2.90)*
New	1.67 (0.96-2.89)	1.65 (0.95, 2.86)	1.65 (0.95, 2.86)	1.63 (0.93, 2.83)
Intermittent	1.74 (1.26-2.40)*	1.68 (1.22, 2.33)*	1.72 (1.24, 2.37)*	1.67 (1.21, 2.31)*
Chronic	2.34 (1.36-4.03)*	2.24 (1.30, 3.86)*	2.25 (1.30, 3.91)*	2.17 (1.25, 3.76)*

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.6 Hazard ratios for the association between affective case history and mortality, adjusted for stressful life events; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)	
	Sex adjusted	Sex + stressful life events
Affective history[a]		
Never	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.97 (1.27, 3.06)*
New	1.67 (0.96-2.89)	1.67 (0.96, 2.91)
Intermittent	1.74 (1.26-2.40)*	1.73 (1.24, 2.42)*
Chronic	2.34 (1.36-4.03)*	2.30 (1.31, 4.02)*

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.7 Hazard ratios for the association between affective case history and mortality, adjusted for adverse childhood experiences (ACEs) ; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)				
	Sex adjusted	Sex + childhood cleanliness	Sex + parental abuse	Sex + divorce	All
Affective history[a]					
Never	ref	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.96 (1.26, 3.04)*	1.97 (1.27, 3.06)*	1.98 (1.28, 3.07)*	1.96 (1.26, 3.04)*
New	1.67 (0.96-2.89)	1.66 (0.96, 2.87)	1.67 (0.96, 2.89)	1.66 (0.96, 2.88)	1.66 (0.96, 2.87)
Intermittent	1.74 (1.26-2.40)*	1.71 (1.24, 2.36)*	1.73 (1.25, 2.39)*	1.74 (1.26, 2.40)*	1.71 (1.24, 2.36)*
Chronic	2.34 (1.36-4.03)*	2.30 (1.33, 3.97)*	2.28 (1.32, 3.96)*	2.27 (1.31, 3.94)*	2.21 (1.27, 3.85)*

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.8 Hazard ratios for the association between affective case history and mortality, adjusted for other childhood factors; based on 235 deaths and 15 imputations (n=3001)

	Hazard ratio (95% CI)				
	Sex adjusted	Sex + Childhood Social class	Sex + Adolescent externalising	Sex + Childhood sickness absence	All
Affective History[a]					
Never	ref	ref	ref	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.89 (1.22, 2.95)*	2.04 (1.31, 3.16)*	1.88 (1.21, 2.92)*	1.88 (1.21, 2.92)*
New	1.67 (0.96-2.89)	1.62 (0.93, 2.81)	1.66 (0.96, 2.88)	1.63 (0.94, 2.83)	1.59 (0.91, 2.76)
Intermittent	1.74 (1.26-2.40)*	1.73 (1.26, 2.39)*	1.71 (1.24, 2.36)*	1.73 (1.25, 2.39)*	1.70 (1.23, 2.35)*
Chronic	2.34 (1.36-4.03)*	2.38 (1.38, 4.09)*	2.24 (1.29, 3.89)*	2.24 (1.29, 3.88)*	2.21 (1.27, 3.85)*

* $p < 0.05$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times.

Table 6.3.7.9 summarises the extent to which the sex adjusted association between affective case history and mortality was explained by each group of covariates (obtained from the 'All' group hazard ratios presented in tables 6.5.3.1-8). Since each covariate group is not independent of one another, these figures provide only an approximate indication of the importance of each group.

Table 6.3.7.9 shows that among those with new, intermittent and chronic caseness, the association between affective case history and mortality was most strongly attenuated by health status variables, health behaviours and psychotropic medication use. In contrast, adolescent only caseness was most strongly attenuated by health status variables, whilst health behaviours appeared to have a slight suppression effect (largely accounted for by smoking, see table 6.3.7.10), and psychotropic medication had no explanatory role.

Across all types of affective case history, more moderate attenuation was observed with respect to social networks, 'other' childhood factors (childhood social class, childhood sickness absence and adolescent externalising), and adult socio-economic factors. Adverse childhood experiences appeared to slightly attenuate associations between chronic affective caseness and mortality, whilst stressful life events had no notable explanatory role.

Table 6.3.7.9 Percentage attenuation of the sex adjusted association between affective case accumulation and mortality by each group of covariates (ordered by total absolute explanatory effect)

	% attenuation[b]			
	Affective case history[a]			
Covariate group	Adolescent only	New	Intermittent	Chronic
Physical health status	26.5	23.9	32.4	53.0
Health behaviours	-7.1	16.4	31.1	44.0
Psychotropic medication	1.0	10.4	24.3	38.1
Social networks	12.2	6.0	9.5	12.7
Other childhood factors	10.2	11.9	5.4	9.7
Adult Socio-economic factors	9.2	9.0	5.4	13.4
Adverse childhood experiences	2.0	1.5	4.1	9.7
Stressful life events	1.0	0.0	1.4	3.0
Fully adjusted (all groups)	23.5	53.7	62.2	85.1

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times

b: % attenuation of each separate group of covariates entered into the sex-adjusted model (different covariate groups were not entered into the model together)

Table 6.5.7.10 and figure 6.3.7.10 summarise the extent to which the sex adjusted association between affective case history and mortality was explained by each individual covariate (obtained from the hazard ratios presented in tables 6.3.7.1-8); however, as mentioned previously, these figures should be interpreted with caution as each covariate is not independent.

Among those with chronic caseness, self-reported health conditions, physical activity, lung function, smoking, anxiolytic use, antidepressant use, eating choices, social class and pulse rate most strongly attenuated associations between affective case history and mortality (>10% attenuation), with a similar trend observed with respect to study members who experienced intermittent caseness.

In contrast, among those with adolescent only caseness, self-reported health conditions, anxiolytic use, and antidepressant use had little or no explanatory role, whilst smoking appeared to demonstrate a relatively strong suppression effect. The association between adolescent only caseness and mortality appeared to be most strongly attenuated by

physical activity, lung function, adult social class, pulse rate, marital status, and childhood sickness absence (>10% attenuation).

Among those who experienced new caseness, the association with mortality was most strongly explained by self-reported health conditions, physical activity, smoking, and antidepressant use; notably however, lung function and eating choices had little or no attenuating effect compared to other types of affective case history.

Table 6.3.7.10 Percentage attenuation of the sex adjusted association between affective case history and mortality, by individual covariates (ordered by total absolute explanatory effect)

	% attenuation[b]			
	Affective case history[a]			
Covariate	Adolescent only	New	Intermittent	Chronic
Self-reported health conditions	5.1	19.4	21.6	32.8
Physical activity	19.4	10.4	14.9	23.9
Lung function	19.4	3.0	18.9	24.6
Smoking	-23.5	14.9	20.3	26.1
Anxiolytic use	0.0	6.0	18.9	30.6
Antidepressant use	1.0	10.4	13.5	21.6
Eating choices	8.2	0.0	12.2	17.2
Adult social class	11.2	9.0	8.1	11.9
Pulse rate	11.2	4.5	4.1	12.7
Marital status	11.2	3.0	8.1	7.5
Childhood sickness absence	10.2	6.0	1.4	7.5
Education	8.2	4.5	1.4	6.7
Childhood social class	9.2	7.5	1.4	-3.0
Social support (friends)	2.0	3.0	2.7	6.7
Adolescent externalising	-6.1	1.5	4.1	7.5
Systolic blood pressure	0.0	-4.5	-2.7	-4.5
Problem drinking	-4.1	0.0	5.4	6.0
Childhood cleanliness	2.0	1.5	4.1	3.0
Body mass Index	-1.0	4.5	2.7	3.7
Parental abuse	1.0	0.0	1.4	4.5
Parental divorce	0.0	1.5	0.0	5.2
Stressful life events	1.0	0.0	1.4	3.0

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times

b: % attenuation of each individual covariate entered separately into the sex-adjusted mode

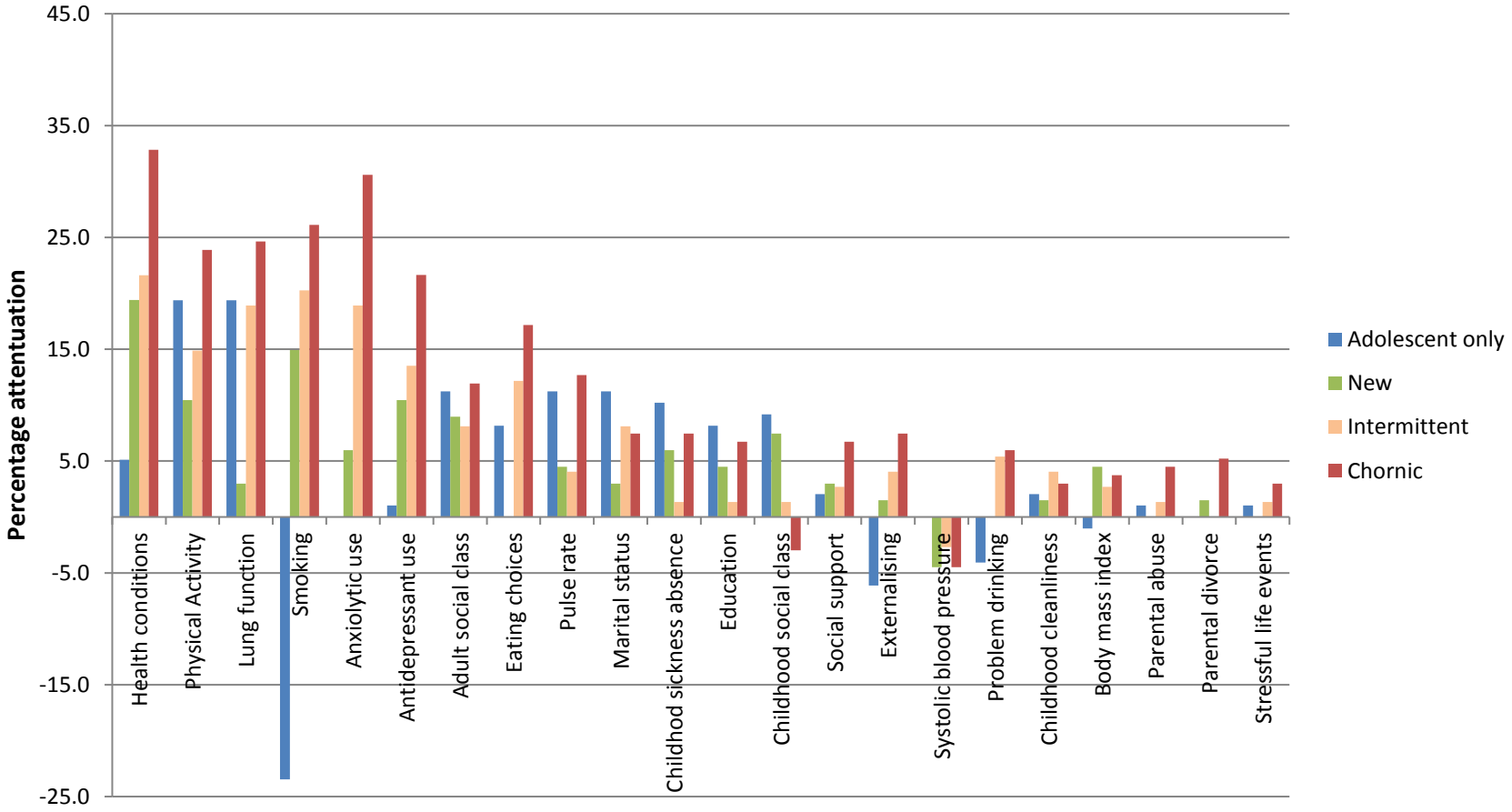

Figure 6.3.7.10 Percentage attenuation of the sex adjusted association between affective case history and mortality, by individual covariates (ordered by total absolute explanatory effect)

Table 6.3.7.11 shows that the sex adjusted associations between mortality and intermittent and chronic caseness were largely attenuated and no longer statistically significant after full adjustment for covariates (attenuated by 62% and 85%, respectively – also see table 6.3.7.9). In contrast, the association between adolescent-only caseness and mortality was only slightly explained (attenuated by 24%), and adolescent-only caseness continued to be associated with a 73% increased risk of mortality.

The sex adjusted hazard ratio for new caseness was not statistically significant and appeared slightly attenuated after full adjustment (54% attenuated).

Table 6.3.7.11 Sex adjusted and fully adjusted hazard ratios for the association between affective case accumulation and mortality; based on 235 deaths and 15 imputations (n=3001)

	Mortality Hazard Ratio (95% CI)	
	Sex adjusted	**Fully adjusted[b]**
Affective case history[a]		
Never	ref	ref
Adolescent only	1.98 (1.27-3.07)*	1.73 (1.10, 2.72)*
New	1.67 (0.96-2.89)	1.32 (0.74, 2.36)
Intermittent	1.74 (1.26-2.40)*	1.27 (0.89, 1.81)
Chronic	2.34 (1.36-4.03)*	1.17 (0.61, 2.23)
Sex		
Male	-	ref
Female	-	0.49 (0.34, 0.70)**
Adult social class		
Professional (I)	-	ref
Intermediate (II)	-	0.83 (0.46, 1.49)
Skilled, non-manual (III-NM)	-	0.74 (0.35, 1.53)
Skilled, manual (III-M)	-	0.94 (0.50, 1.76)
Partly skilled (IV)	-	1.10 (0.54, 2.24)
Unskilled (V)	-	0.94 (0.40, 2.19)
Education		
None	-	ref
O-level or equivalent	-	1.37 (0.96. 1.96)
A-level or equivalent	-	1.17 (0.76, 1.79)
Higher education	-	1.73 (0.91, 3.27)
Systolic blood pressure (mmHg)		
Per standard deviation	-	0.97 (0.82, 1.14)
Lung function (FEV_1)		
Per litre	-	0.66 (0.51, 0.86)**
Pulse rate (bpm)		
Per standard deviation	-	1.37 (1.20, 1.57)**
Body mass index (kg/m^2)		
Per standard deviation	-	1.09 (0.95, 1.26)
Health conditions		
0	-	ref
1	-	1.14 (0.79, 1.64)
2	-	1.68 (1.11, 2.55)*
3 or more	-	2.01 (1.18, 3.42)*

Smoking		
Never smoked	-	ref
Predominantly non-smoker	-	1.27 (0.84, 1.93)
Predominantly smoker	-	1.82 (1.19, 2.80)*
Lifetime smoker	-	2.24 (1.42, 3.53)**
Problem drinking		
No	-	ref
Yes	-	1.16 (0.80, 1.69)
Physical activity		
Inactive	-	ref
Least active	-	0.70 (0.50, 0.98)*
Most active	-	0.67 (0.44, 1.02)
Eating Choices Index		
Per unit	-	0.96 (0.82, 1.14)
Antidepressant use		
No	-	ref
Yes	-	1.03 (0.62, 1.71)
Anxiolytic use		
No	-	ref
Yes	-	1.30 (0.82, 2.06)
Marital status		
Married or cohabiting	-	ref
Single	-	1.69 (1.02, 2.82)*
Divorced, widowed, separated	-	1.31 (0.87, 1.95)
Social support (friends)		
Always	-	ref
Often/sometimes/never	-	1.06 (0.76, 1.46)
Stressful life events		
0-5	-	ref
6-9	-	0.86 (0.61, 1.21)
10+	-	0.98 (0.59, 1.65)
Parental divorce		
No	-	ref
Yes	-	1.13 (0.66, 1.94)
Childhood cleanliness		
Amongst the best/average	-	ref
Amongst the worst	-	0.98 (0.46, 2.12)
Parental abuse		
No	-	ref
Yes	-	1.11 (0.63, 1.95)
Childhood social class		
Professional (I)	-	ref
Intermediate (II)	-	2.17 (0.91, 5.18)
Skilled, non-manual (III-NM)	-	2.15 (0.90, 5.16)

Skilled, manual (III-M)	-	1.82 (0.77, 4.29)
Partly skilled (IV)	-	2.49 (1.03, 5.98)*
Unskilled (V)	-	2.01 (0.76, 5.33)
Adolescent externalising		
Mild	-	ref
Moderate	-	0.88 (0.59, 1.32)
Severe	-	1.23 (0.75, 2.02)
Childhood sickness absence (weeks)		
0-4	-	ref
4-10	-	1.06 (0.76, 1.46)
10+	-	1.72 (1.15, 2.56)*

* $p < 0.05$

**$p < 0.001$

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); Chronic = case 3-4 times

b: mutually adjusted estimates

6.4 Discussion

Over a fifteen year follow-up and after adjustment for sex, adolescent only, intermittent, and chronic caseness were all associated with an increased risk of mortality; the hazard ratio for new caseness was also raised although the association was not statistically significant.

New caseness

Markedly, exploratory analyses revealed that new caseness was associated with over three-times the risk of mortality in the first 4 years of follow-up, but demonstrated no association in later years. Furthermore, over the full fifteen year follow-up, the hazard ratio for new caseness was attenuated after the inclusion of a three-year wash-out period. These results were consistent with the idea of reverse-causality, whereby poor physical health may lead to affective symptoms through psychological pathways, such as feeling of hopelessness, impending doom, or difficulties meeting personal goals, and through inflammatory pathways – where pro-inflammatory cytokines act directly on the brain eliciting depressive behaviour (Capuron et al., 2004; Dantzer et al., 2007; Poole et al., 2011).

Over a four-year follow-up, the mortality risk associated with new caseness was similar to that found for chronic caseness, which is at odds with the dose-dependent relationship between affective caseness and mortality highlighted in chapter 5. Notably, the results followed an identical trend to that reported by Penninx et al., (1998b) who found that in a community-based sample of older persons, chronic and new-onset depressive caseness were equally associated with mortality over a four-year follow-up (age and sex adjusted HR: 1.73, 95% CI 1.36–2.20 and HR=1.73 95% CI 1.32–2.25, respectively). Likewise, over a fifteen month follow-up, Bruce & Leaf (1989) found that 'recent' affective disorder was if anything, more strongly associated with mortality compared to lifetime disorder.

Notably, Penninx et al., (1998b) also found that new-onset symptoms appeared to be a slightly stronger predictor of cardiovascular events and mortality compared to chronic symptoms, particularly among males. This implies that the associations between new-onset caseness and mortality might be dependent on the cause of death, which is examined in the following chapter. There was no evidence of a sex interaction in the current analysis between affective case history and mortality (joint Wald test, p=0.27).

Unfortunately, there were too few deaths within the first four years of follow-up to be able to conduct meaningful multivariable analysis. Over the full fifteen year follow-up, the association between new caseness and mortality was most strongly attenuated by self-reported health conditions, followed by smoking, physical activity and antidepressant use. Since 'new' caseness occurred immediately prior to follow-up, this suggests that self-reported health conditions, smoking, and physical activity are upstream of affective symptoms – and again indicative of reverse causality. For example, smoking and low levels of physical activity may lead to poor physical health (Doll et al., 2004; Paffenbarger Jr et al., 1993), which in turn may lead to affective symptoms though psychological and/or inflammatory pathways (Capuron et al., 2004; Dantzer et al., 2007; Poole et al., 2011).

In contrast, antidepressants are likely to mediate associations with mortality through their effects on physical health (Grossman and Messerli, 2012; Hamer et al., 2010a; Licht et al., 2009; Thase, 1998), or could simply act as an over-adjustment (as discussed previously). Notably, by age 53 a much larger proportion of antidepressant prescriptions in the NSHD were for SSRI's (42%), which have been associated with fewer side effects compared to earlier types of mediation (Sauer et al., 2001; Taylor et al., 2005; Vogelzangs et al., 2012). This could therefore suggest that controlling for antidepressants might be more likely to be an over-adjustment. Equally however, it is possible that the 'new' caseness group contained those who had previously taken psychotropic medication, or had a history of affective symptoms which was not captured in the NSHD. Additional bivariate analyses were conducted to explore what proportion of those who were a 'new' case had taken psychotropic medication prior to age 53: among those with 'new' caseness, 8.6% had reported antidepressant or anxiolytic medication use at ages 26, 36, or 43. Although antidepressant medication may also be prescribed for conditions such as substance abuse, eating disorders, and chronic or neuropathic pain (British Medical Association & Pharmaceutical Society of Great Britain (2002), it is likely that the 'new' caseness group included a substantial number of individuals who were an affective case on multiple occasions. This makes it difficult to accurately interpret explanatory pathways; however potential misclassification could also suggest that the association between new caseness and mortality is if anything, an underestimate.

Unusually, unlike other types of affective case history, lung function and eating choices had no notable explanatory role. This supports the idea of a distinct explanatory pathway between new caseness and mortality, compared to other types of affective case history.

Adolescent only caseness

After full adjustment for all covariates, the association between adolescent-only caseness and mortality was largely unexplained; those who were a case in adolescence-only continued to have a 73% increased risk of mortality compared to those who were never a case. In contrast, all other types of affective case history demonstrated considerable attenuation and were no longer statistically significant after full adjustment.

Multivariable analyses demonstrated that the relationship between adolescent-only caseness and mortality was most strongly explained by physical activity, lung function, adult social class, pulse rate, marital status, and childhood sickness absence; however, in contrast to all other types of affective case history, self-reported health conditions, anxiolytic use, and antidepressant use had little or no explanatory role, whilst smoking appeared to demonstrate a considerable suppression effect. These results suggest that the mechanism underlying the relationship between adolescent-only caseness and mortality is different compared to other types of affective case history.

It might be expected that emotional problems in adolescence could, for example, influence mortality through their impact educational attainment (Richards and Abbott, 2009) and the formation of lifelong detrimental health behaviours (Breslau et al., 1998; Fuller-Thomson et al., 2013). However, the association between adolescent-only caseness and mortality was only slightly explained by educational attainment and diet, whilst smoking, and to a much lesser extent problem alcohol, actually acted as negative confounders.

Physical inactivity partially explained the association; however there was evidence to suggest that this could be a proxy for poor physical health. For example, bivariate analyses showed those who were an affective case in adolescence-only appeared to have relatively low levels of physical activity, yet were least likely to smoke or have alcohol problems, and had the lowest BMI – which is unusual given the tendency of health behaviours to cluster (Burke et al., 1997; Conry et al., 2011).

It is likely that lung function and pulse rate confound the association between adolescence-only caseness and mortality, as it seems doubtful that a single affective case in adolescence could lead to relatively poor lung function and high pulse rate in adulthood, especially since those with adolescent-only caseness had a relatively healthy lifestyle.

Childhood sickness absence also appeared to attenuate the association between adolescent-only caseness and mortality. Notably, bivariate analyses demonstrated that

those with adolescent-only caseness had the highest levels of childhood sickness absence. The 'Protection Motivation Theory' (Maddux and Rogers, 1983; Rogers, 1975) suggests that if an individual perceives themselves as vulnerable to a serious health threat, this will increase their motivation to engage in protective behaviours, which could help to explain the comparatively healthy lifestyle among those with adolescent-only caseness. Equally, it is possible that those with anxiety and depressive symptoms could be generally more risk averse (Richards and Abbott, 2009); however this does not explain why those with chronic caseness had particularly strong associations with poor health behaviours (see table 6.3.6), since over half of study members in this group first experienced affective caseness in adolescence (see table 5.3.6.2).

Somewhat surprisingly, the association between adolescent-only caseness and mortality did not appear to be explained by self-reported chronic health conditions, which included cancer, heart problems, stroke, diabetes, bronchitis, and blood pressure problems.

Marital status partially explained the association between adolescent-only caseness and mortality, probably though mediation. Bivariate analyses showed that those with adolescent-only caseness had the highest likelihood of being single (never married), which was in turn associated with an increased risk of mortality compared those who were married or co-habiting. Notably, this contrasts with the explanatory pathway discussed in chapter five with respect to those who experienced multiple affective caseness, who were far more likely to have experienced the strain associated with divorce, separation or widowhood, compared to those who were a case at a single point in time (see section 5.4.2).

Adult social class had no notable explanatory effect when health behaviours and health status variables were included in the model (not shown). As discussed previously in section 5.4.2, the attenuating effect of adult social class is likely to be explained by social gradients in smoking, diet, physical activity, and health (Ferrie et al., 2002; Marmot et al., 1991).

In contrast to those who experienced an affective case on multiple occasions (2 or 3-4 times; see section 5.4.2 for discussion of explanatory factors), it could be speculated that the association between adolescent-only caseness and mortality is potentially driven by factors related to poor physical health in early-life – as implied by the relatively positive health behaviours and high levels of childhood sickness absence in this group.

Markedly however, after fully adjustment, there was a considerable residual association between adolescent-only caseness and mortality, with 76% of the association unexplained; this suggests that there could be other important factors, which were not accounted for in this thesis that might better explain the association.

No other studies have explored the association between mortality and affective symptoms occurring only in adolescence, so it is not possible to directly compare the results with previous findings.

Across all types of affective case history, education, childhood social class, social support from friends, adolescent externalising, systolic blood pressure, problem alcohol, body-mass-index, adverse childhood experience variables, and stressful life events had relatively little attenuating effect compared to all other covariates, which suggests that these variables were not notable confounders or mediators. Please refer to chapter five, section 5.4.2, for further discussion of these variables.

Multivariable analyses with respect to chronic caseness (those who were an affective case 3-4 times) has been previously discussed in detail in chapter 5. Intermittent caseness captured all those who were a case at one or two time points, and who didn't experience chronic, new, or adolescent-only caseness. Due to low power, it was not possible to breakdown intermittent caseness into further sub-categories, which means that a thorough discussion based-on the timing of symptoms is not possible. As might be expected, intermittent caseness demonstrated a pattern of attenuation across multivariable models consistent with those previously observed in those who were an affective case one to two times (see sections 5.3.12.9-10).

Limitations

The measure of affective case history is likely to contain a considerable amount of noise, as highlighted earlier with regard to 'new' caseness. It is unlikely that the four measures of affective symptoms used in the NSHD will give an accurate history of lifetime affective symptoms as they capture only a relatively short window of time.

It should also be noted that affective symptoms at age 13-15 were rated by teachers, and so was the only measure in the NSHD that was not self-reported. As such, it is possible that adolescent-only caseness captured a slightly different construct compared the other measures, although teacher-rated and self-report data have been shown to have similar levels of validity when screening for child psychiatric disorders (Goodman, 2000).

Nevertheless, the factor structure of affective symptoms assessed at age 13-15 was consistent with all other types of affective symptom measure used in the NSHD (see section 3.4.9), suggesting that they was an underlying similarity across the main exposures.

6.5 Summary

Over a fifteen year follow-up and after adjustment for sex, adolescent-only, intermittent and chronic caseness were associated with an increased risk of mortality compared to those who were never a case. The hazard ratio for new caseness was raised, although the association was not statistically significant. Notably, the inclusion of a three-year wash-out period attenuated the hazard ratio for new caseness, which is consistent with reverse causality with poor physical health. Furthermore, over a four-year follow-up, new caseness was associated with over three times the risk of mortality compared to those who were never a case whilst there was no association in later years.

Over a fifteen year follow-up, multivariable analysis showed that the new caseness hazard-ratio was most strongly attenuated by self-reported health conditions, followed by smoking, physical activity and antidepressant use. It is likely that self-reported health, smoking, and physical activity acted as confounders, whilst antidepressant use was either a mediator or an over-adjustment.

After full adjustment, adolescent-only caseness was associated with a 74% increased risk of mortality compared to those who were never a case. In contrast, all other types of affective case history were largely attenuated and no longer statistically significant. There was evidence to suggest that the relationship between adolescent-only caseness and mortality was spurious, and perhaps driven by poor physical health in childhood.

The association between adolescent-only caseness and mortality was most strongly explained by lung function, physical activity, adult social class, pulse rate, marital status, and childhood sickness absence. The results suggested that marital status (being single) was likely to be a mediator, whilst all other factors were probably confounders; a single affective case in adolescence was unlikely to lead physical inactivity over the life course, and poor lung function and high pulse rate in adulthood. In contrast to all other types of affective case history, smoking appeared to have a relatively strong suppression effect, as those who were a case in adolescence-only were least likely to smoke.

Notably, the hazard ratios for new and adolescence-only caseness appeared to be most strongly attenuated by a different set of covariates compared to those with intermittent or chronic caseness (or those who were an affective case two or more times – as discussed in section 5.4.2); this could suggest that different types of affective case history may have unique pathways to mortality. For example, in contrast to all other types of affective case history, the hazard ratio for adolescent-only caseness was not attenuated by self-reported health conditions, whilst new caseness was not attenuated by lung function. This could also imply that different types of affective case history might be more strongly associated with particular causes of death. The relationship between lifetime affective caseness and cause-specific mortality is examined in the following chapter.

7. AFFECTIVE CASE ACCUMULATION AND AFFECTIVE CASE HISTORY BY CAUSE OF DEATH

7.1 Chapter overview

This chapter presents the results of analyses relating primarily to objective 2.3: To investigate the association between lifetime affective caseness and mortality with respect to cause-specific mortality (cancer, cardiovascular, externalising, and other causes).

The following hypothesis was tested:

2.3 Affective caseness will be associated with mortality across all causes of death, particularly cardiovascular deaths

This chapter includes the results of additional analyses using imputed data, which examines whether the association between mortality and affective case accumulation and affective case history is cause-specific. These analyses were conducted in order to identify possible trends which could help provide further insight into potential explanatory pathways; however the results should be interpreted with caution due to very low power to detect small or moderate effects, which also meant that it was not possible to conduct comprehensive multivariable analyses (conducting analyses by cause-of-death leads to a further reduction in power compared to all-cause mortality – see power tables 5.3.7 and 6.3.4).

This chapter first presents descriptive characteristics of affective case accumulation and affective case history by cause-of-death. Secondly, sex adjusted analyses are shown for the association between mortality and affective case accumulation and affective case history by cause of death, which is then followed by a discussion of the results.

7.2 Methods

7.2.1 Exposure variable

The main exposure variables used in this chapter are affective case accumulation and affective case history, derived from the affective 'case' variables at ages 13-15, 36, 43, and 53 (described in detail in section 3.4). An affective case refers to those who experienced

severe affective symptoms, and 'never' and 'chronic' caseness are identical to those who were a case 0 and 3-4 times, respectively.

7.2.2 Outcome variable

The outcome variable is cause-specific mortality (as described previously in section 3.5), with follow-up from age 53 onwards. There were 235 deaths including cancer (n=114), cardiovascular disease (n=57), externalising deaths (n=20), and 'other' causes (n=40; see table 7.3.2.2 for a detailed breakdown).

7.2.3 Analytical strategy

The associations between cause-of-death and affective case accumulation, and affective case history were assessed using the imputed data.

Descriptive analyses were conducted to demonstrate the prevalence of cardiovascular, cancer, externalising and other deaths by affective case accumulation and affective case history.

Since cause-of-death is mutually exclusive, competing-risks analyses were used to examine the sex adjusted associations between affective case accumulation and affective case history and cardiovascular, cancer, externalising, and other deaths. Sex interactions were tested using the joint Wald test; across all causes of death, there was no evidence of a sex interaction with respect to either affective case accumulation or affective case history (joint Wald tests, $p>0.05$).

Sex adjusted competing-risks analyses were also performed on the original (non-imputed) data; however power was too low to explore the relationship between affective case accumulation and affective case history and externalising deaths (n=8) (see Appendices N and O).

7.3 Results: Sex adjusted associations between mortality and affective case accumulation and affective case history by cause of death

7.3.1 Participants

The study sample is identical to that used in the previous two chapters (see figure 5.3.1)

7.3.2 Descriptive characteristics of cause of death by sex

Table 7.3.2.1 shows that cancer was the most common cause of death, followed by death from cardiovascular disease (CVD), other, and externalising causes. Males were more likely to die from cardiovascular disease and externalising causes, whilst females were more likely to die from cancer and other causes. These trends were similar to those seen in the non-imputed data (see Appendix M).

Table 7.3.2.1 Mortality from age 53 onwards by cause of death and sex (imputed data, n=3001)

	All		Males	Females
Cause of death	n	%	%	%
Cancer	118	50.2	48.9	52.0
CVD	57	24.3	25.6	22.6
Other	40	17.0	15.8	18.6
Externalising	20	8.5	9.8	6.9
Total	235	100	100	100

Table 7.3.2.2 shows that of those who died from other causes, the majority (65%) were accounted for by disease of the respiratory system and diseases of the digestive system.

Table 7.3.2.2 Detailed breakdown of 'other' causes of death

Other causes of death (specified)	**n**	**%**
Diseases of the respiratory system	14	35
Diseases of the digestive system	12	30
Diseases of the nervous system	7	17.5
Diseases of the genitourinary system	3	7.5
Certain infectious and parasitic diseases	1	2.5
Endocrine, nutritional and metabolic diseases	1	2.5
Not elsewhere classified	1	2.5
Diseases of the musculoskeletal system and connective tissue	1	2.5
Total	**40**	**100**

7.3.3 Descriptive characteristics of cause of death by affective case accumulation and affective case history

Figure 7.3.3.1 shows that as affective caseness increases, the proportion of cancer deaths appears to decrease, whilst the proportion of deaths from 'other' causes increases. Deaths from cardiovascular disease and externalising causes appear to be relatively consistent irrespective of case accumulation.

Figure 7.3.3.2 shows that the cause of death appears to vary by affective case history. Those with new caseness appear to have the highest proportion of cardiovascular deaths, whilst those with adolescent-only caseness have the highest proportion of cancer deaths. Deaths from 'other' causes appear most common among those with chronic, intermittent and new caseness, whilst externalising deaths appear least common among adolescent-only caseness, compared to all other types of case history.

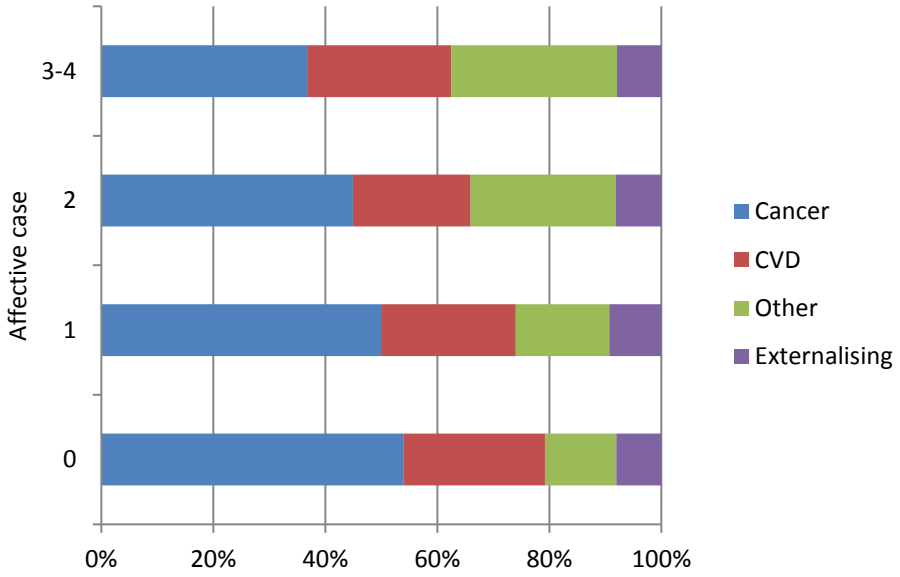

Figure 7.3.3.1 Cause of death by affective case accumulation, based on 235 deaths

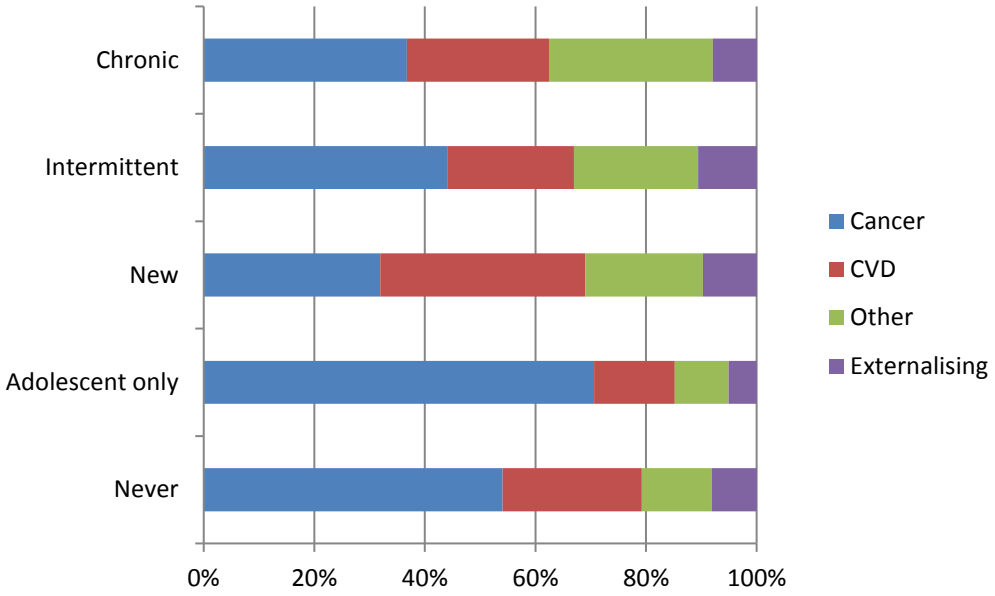

Figure 7.3.3.2 Cause of death by affective case history, based on 235 deaths

7.3.4 Sex adjusted associations between mortality and affective case accumulation and affective case history by cause of death

Table 7.3.4.1 shows that after adjustment for sex, the sub-distribution hazard ratios (SHRs) or mortality were raised across all causes of death. There was a particularly strong association between affective caseness and mortality from 'other' causes of death, whereby the risk of mortality appeared to increase as affective caseness increased. There was also a statistically significant association between those who experienced a single affective case and cancer mortality. The affective case accumulation SHRs appeared to be slightly larger with regard to cardiovascular mortality compared to cancer mortality; although the associations were not statistically significant.

Table 7.3.4.1 Sex adjusted sub-distribution hazard ratios (SHRs) for the association between affective case accumulation and mortality, by cause of death (n=3001)

	SHR (95% CI)			
	Cardiovascular disease (57 deaths)	**Cancer** (118 deaths)	**Externalising** (20 deaths)	**Other** (40 deaths)
Affective case				
0	ref	ref	ref	ref
1	1.66 (0.88, 3.14)	1.59 (1.05, 2.43)*	2.07 (0.73, 5.86)	2.25 (1.03, 4.93)*
2	1.56 (0.59, 4.10)	1.49 (0.76, 2.93)	1.90 (0.33, 10.90)	3.69 (1.35, 10.14)*
3-4	2.37 (0.85, 6.60)	1.49 (0.58, 3.81)	2.36 (0.29, 19.41)	5.26 (1.90, 14.90)**

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

Table 7.3.4.2 shows that after adjustment for sex, new affective caseness was associated with an increased risk of cardiovascular mortality, but there was no evidence of an association with cancer mortality. The sub-distribution hazard ratios for new caseness were also raised for externalising and 'other' deaths, although these associations were not statistically significant. In contrast, adolescent only caseness was associated with an increased risk of cancer mortality, but there was little evidence of an association with respect to cardiovascular or externalising deaths. The SHRs for intermittent and chronic caseness were raised across all causes of death, but were only statistically significant for 'other' causes of death.

Table 7.3.4.2 Sex adjusted sub-distribution hazard ratios (SHRs) for the association between affective case history and mortality, by cause of death (n=3001)

	SHR (95% CI)			
	Cardiovascular disease (57 deaths)	**Cancer** (118 deaths)	**Externalising** (20 deaths)	**Other** (40 deaths)
Affective case history[a]				
Never	ref	ref	ref	ref
Adolescent only	1.12 (0.37, 3.39)	2.57 (1.50, 4.41)*	1.19 (0.17, 8.53)	1.45 (0.38, 5.59)
New	2.46 (1.01, 5.95)*	0.95 (0.39, 2.27)	1.97 (0.31, 12.54)	2.70 (0.78, 9.28)
Intermittent	1.58 (0.81, 3.09)	1.37 (0.85, 2.20)	2.40 (0.83, 6.95)	3.01 (1.38, 6.60)*
Chronic	2.38 (0.85, 6.62)	1.48 (0.58, 3.79)	2.38 (0.29, 19.54)	5.26 (1.89, 14.59)**

* $p < 0.05$
** $p < 0.001$
a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); chronic = case 3-4 times

7.4 Discussion

The results presented in this chapter are suggestive of several trends; however they should be interpreted with caution due to low power across all analyses.

The sex adjusted sub-distribution hazard ratios (SHRs) for affective case accumulation and affective case history were raised across all causes of death, which is consistent with previous research; associations between affective symptoms and mortality have been shown with respect to cancer (Chida et al., 2008), cardiovascular disease (Penninx et al., 1998b; Wulsin et al., 1999), respiratory diseases, diseases of the metabolism, and accidental death and suicide (Mykletun et al., 2007).

The SHRs for affective case accumulation and affective case history appeared to be slightly larger for cardiovascular mortality compared to cancer mortality; however the strongest associations were observed with regard to deaths from 'other' causes, particularly among those who were an affective case 3-4 times/chronic caseness. 'Other' causes of death included diseases of the respiratory system (35%), digestive system (30%), nervous system (17.5%), and all other causes (17.5%) (see table 7.3.2.2 for further breakdown). It is likely that diseases of the respiratory system are partially accounted for by smoking (Centers for Disease Control and Prevention, 2004), although it is less clear why affective symptoms would be associated with diseases of the digestive and nervous systems. Notably, additional investigation found that only two deaths were accounted for by liver disease/liver failure which is consistent with the negligible explanatory role of alcohol problems discussed in chapters 5 and 6.

The large majority of previous studies examining the relationship between affective symptoms and cause-specific mortality have focused on cancer and cardiovascular mortality. The literature has tended to show more consistent and larger associations between affective symptoms and cardiovascular mortality compared to cancer mortality, which is in line with the current analyses.

Only one study appears to have assessed the relationship between affective symptoms and mortality across multiple causes of death. Among a large Norwegian community-based sample, Mykletun et al., (2007) found that depressive symptoms were most strongly related to deaths from suicide, diseases of the nervous system, metabolic diseases, and respiratory disease, whilst smaller effects were observed with respect to deaths from cardiovascular disease and cancer. It was not possible to assess the relationship between

affective symptoms and suicide (n=5) in the NSHD due to low numbers. Otherwise, the findings of Mykletun et al., (2007) are largely consistent with the current analyses, showing that the strongest associations were observed with respect to deaths from 'other' causes.

Adolescent-only and new caseness appeared to be associated with different causes of death; for example new caseness was associated with an increased risk of death from cardiovascular disease, but not cancer; conversely, adolescent only caseness was associated with an increased risk death from cancer, but not cardiovascular disease. This implies that adolescent-only and new caseness may have distinct pathways to mortality. These finding are also consistent with the results of multivariable analyses in chapter 6 – showing that the associations between mortality and adolescent-only and new caseness were explained by different covariates.

The association between adolescent-only caseness and cancer mortality raised the question as to whether this group had a higher likelihood of experiencing childhood cancer. Chapter five demonstrated that the association between adolescent-only caseness and all-cause mortality was only marginally attenuated by 'number of health conditions', which included cancer; however this variable was a composite measure which could feasibly mask the role of individual conditions. As such, additional analyses were conducted (not shown) which found that those with adolescent-only caseness were no more likely to have experienced cancer prior to follow-up compared to other types of affective case history.

Study members who experienced adolescent-only caseness appeared to have relatively good health behaviours (see table 6.3.6), which suggests that the increased risk of cancer is unlikely to be driven by lifestyle factors. It is perhaps more likely that among those with adolescent-only caseness a greater role may be played by factors such as genetic vulnerability, or exposures earlier in life, such as infection by Helicobacter Pylori, which has been linked with gastric cancer (Uemura et al., 2001). Markedly, further investigation revealed that those with adolescent-only caseness were not dying of any particular type of cancer, which could point towards a generic explanatory mechanism.

Study members who experienced 'new' caseness appeared to have a higher risk of cardiovascular disease, compared to those who were never a case. This is consistent with Penninx et al. (1998b), who found that in a community-based study of older persons, newly depressed mood was associated with a 77% increased risk of cardiovascular mortality after adjustment for age and sex (RR=1.77, 95% CI: 1.25-2.51), as well as increased risk of

cardiovascular events. These associations were stronger among males than females, although in the current analyses there was no evidence of a sex interaction, probably due to low power. Notably, the results also appear to support the theory of 'vascular depression' (Alexopoulos et al., 1997; Baldwin and O'Brien, 2002; Baldwin and Tomenson, 1995), which proposes that depressive symptoms emerging in late-adulthood may encompass a sub-type of depression caused by cerebrovascular disease.

The findings suggest that newly emerging affective symptoms could be particularly important with respect to cardiovascular mortality; however, it was not possible to make inferences about whether new caseness was also associated with externalising and 'other' causes of death because of low power.

As discussed in chapter 6, the relationship between new caseness and all-cause mortality was most strongly explained by 'number of health conditions', which included 'heart trouble' and 'high blood pressure', which as mentioned in earlier chapters, may lead to affective symptoms through psychological or inflammatory pathways (Capuron et al., 2004; Dantzer et al., 2007; Poole et al., 2011); for instance, underlying atherosclerosis is associated with inflammation (Epstein and Ross, 1999), which could lead to the emergence of affective symptoms.

7.4.1 Summary

After adjustment for sex, affective case accumulation and affective case history appeared to be associated with mortality across multiple causes of death. Consistent with previous studies, there was a suggestion of a slightly stronger association between affective caseness accumulation and cardiovascular mortality than cancer mortality; however the strongest associations appeared to be with deaths from 'other' causes, particularly among those who were a case 3-4 times/chronic caseness.

These results also highlight the importance of affective symptom timing, and provide further evidence that adolescent-only and new caseness may have different pathways to mortality; for example, new caseness appeared to be associated with an increased risk of cardiovascular mortality, but not cancer mortality; whilst adolescent-only caseness was associated with an increased risk of cancer mortality, but not cardiovascular mortality.

8. DISCUSSION

This chapter will begin by summarising the results with reference to the objectives described at the beginning of this thesis. Key themes will be identified, as well as a discussion of the strengths and limitations of the analyses. Finally, avenues for future research, policy implications and an overall conclusion are presented.

8.1 Summary of findings

The aim of this thesis was to firstly investigate the nature of the association between affective symptoms and mortality over the life course, and secondly to investigate the explanatory roles of a range of social, behavioural and physiological factors.

8.1.1 Affective symptoms and mortality by age, severity, and type of symptom

Objective 1 aimed to investigate the association between affective symptoms and mortality with respect to i) age (ages 13-15, 36, 43, and 53 years); ii) symptom severity (mild, moderate, severe); and iii) symptom type (anxiety, depressive).

After adjustment for sex, severe affective symptoms across ages 13-15, 36, 43 and 53 were associated with an increased rate of mortality compared to those with no/mild symptoms, although at age 36 the association was not statistically significant. Kaplan Meier survival curves were consistent with an influence of affective symptoms persisting for many years.

At all ages, severe symptoms were more strongly related to mortality compared to moderate symptoms. Notably however, the accumulation of moderate symptoms over the life course did not increase the rate of mortality compared to no/mild symptoms. This implied that severe or 'case-level' symptoms were driving associations with mortality.

Anxiety and depressive symptoms were equally predictive of mortality, suggesting that it was appropriate to treat affective symptoms as a single construct.

Sensitivity analyses demonstrated that across all ages, excluding externalising deaths did not explain associations between affective symptoms and mortality, suggesting that the associations were primarily driven by natural causes of death.

8.1.2 Lifetime affective caseness and mortality

Objective 2 aimed to investigate the association between lifetime affective caseness and mortality with respect to: i) affective caseness accumulation; ii) affective case history (adolescent-only, new-onset, intermittent, and chronic caseness); and iii) cause-specific mortality (cancer, cardiovascular, externalising, and other causes of death).

After adjustment for sex, there was evidence of a dose-response relationship where the risk of mortality appeared to increase with greater caseness accumulation.

Adolescent-only, intermittent and chronic caseness were associated with an increased risk of mortality compared to those who were never a case. New-caseness (those who were a case at age 53 only) was associated with a considerably increased risk of mortality in the first four-years of follow-up, but not in later years – which was suggestive of reverse causality with poor physical health. Notably, the hazard ratios for new and chronic caseness were similar in magnitude, suggesting that the relationship between affective caseness and mortality is not solely determined by accumulation.

Affective case accumulation and affective case history appeared to be associated with mortality across multiple causes of death. There was a slightly stronger association between affective case accumulation and cardiovascular mortality, compared to cancer mortality; however the strongest associations were with respect to deaths from 'other' causes, particularly among those with chronic caseness. Markedly, new caseness was associated with an increased risk of cardiovascular mortality, but not cancer mortality; this was consistent with the theory of 'vascular depression', which proposes that late-onset depression could be due to underlying cerebrovascular disease (Alexopoulos et al., 1997; Baldwin and O'Brien, 2002; Baldwin and Tomenson, 1995). Conversely, adolescent-only caseness was associated with an increased risk of cancer mortality, but not cardiovascular mortality; this implied that adolescent-only and new caseness could have unique pathways to mortality.

Across all analyses, women had a greater likelihood of experiencing severe affective symptoms or caseness; although there was no evidence that the relationship between affective caseness and mortality was different in men and women.

8.1.3 Lifetime affective caseness and mortality – explanatory factors

Objective 3 aimed to investigate to what extent the relationship between lifetime affective caseness and mortality could be explained by the following factors: i) physical health status (number of health conditions and clinical measures); ii) health behaviours (smoking, alcohol consumption, physical activity, and diet); iii) psychotropic medication use (anxiolytics, antidepressants); iv) social networks (marriage, friends); v) stressful life events; and vi) adverse childhood experiences (parental divorce, parental abuse, neglect).

After full adjustment for covariates, the positive associations between mortality and those who were a case 2-4 times, and those with intermittent and chronic caseness (3-4 times a case) were largely explained and no longer statistically significant. In contrast, the associations between mortality and affective caseness at a single time-point and adolescent-only caseness were only partially explained, and continued to be associated with a 46% and 73% increased risk of mortality, respectively, compared to those who were never a case.

Different factors appeared to attenuate the relationship between mortality and affective case accumulation and affective case history dependent on the timing and duration of symptoms. Covariates were considered to attenuate the association if they accounted for at least a 10% reduction in the hazard ratio.

The association between mortality and those who were an affective case 3-4 times (chronic caseness), was most strongly attenuated by number of health conditions, followed by lung function, physical activity, anxiolytic use, smoking, diet, antidepressant use, diet, pulse rate, and adult social class. Similarly, the association between those who were a case two times and mortality followed an almost identical pattern of attenuation. In contrast however, the association between mortality and those who were a case at a single time-point was attenuated by only three variables: number of health conditions, lung function and physical activity. This indicated that those with multiple caseness were likely to have different, or additional pathways to mortality compared to those with single caseness. For example, it is possible that the role of behavioural and socio-economic factors is increased with greater exposure to affective symptoms.

To gain further insight into explanatory mechanisms with regard to those who were a single case, it was necessary to examine the timing of affective caseness.

Whilst only partially explained, the association between adolescent-only caseness and mortality was most strongly attenuated by lung function and physical activity, followed by adult social class, pulse rate, marital status, and childhood sickness absence. Notably, smoking had a considerable suppression effect as study members who had adolescent-only caseness were least likely to smoke – consistent with earlier findings by Richards and Abbott (Richards and Abbott, 2009).

The sex adjusted association between new caseness and mortality was not statistically significant over the full fifteen year follow-up; however the hazard ratio was still attenuated, most strongly by number of health conditions, followed by smoking, physical activity and antidepressant use. It was not possible to conduct multivariable analyses in the first four years of follow-up due to low power.

The pattern of covariate attenuation among those with adolescent-only and new caseness was markedly different. Together with the results for cause-specific mortality, these findings further suggest that adolescent-only and new caseness may have different pathways to mortality.

Several variables appeared to have little or no explanatory role for the association between mortality and affective case accumulation, and affective case history: BMI, systolic blood pressure (which demonstrated a slight suppression effect), problem drinking, social support from friends, stressful life events, and adverse childhood experiences, including parental divorce, parental abuse, and childhood cleanliness (as discussed in detail in section 5.4.2). Furthermore, adjusting for externalising behaviour (conduct problems) and excluding schizophrenia cases had little explanatory effect, suggesting that the relationship between mortality and affective case accumulation and history was not confounded by co-morbid mental health problems.

8.1.4 Explanatory pathways

The results suggested that those with multiple and single affective caseness were likely to have different pathways to mortality, and in addition, among those with single caseness, adolescent-only and new caseness were also likely to have distinct explanatory mechanisms.

Several inferences were made about potential pathways based on the timing of affective symptoms and the nature of covariates attenuating the relationship with mortality. Conceivable pathways are addressed below with respect to the covariates that most strongly attenuated the hazard ratios for chronic (3-4 times a case), adolescent-only, and new caseness. Potential mediators and confounders are speculated; although it should be noted that most covariates are likely to have a bidirectional relationship with affective caseness over time. It was not possible to accurately infer explanatory pathways with regard to those who were a case two times and those with intermittent caseness as there was considerable heterogeneity regarding the timing of affective cases in these groups (see table 5.3.6.2).

Chronic caseness

Among those who were a case 3-4 times (chronic caseness), affective symptoms were likely to have originated relatively early in the life course (see section 1.2.3 and table 5.3.6.2), which suggested that health conditions, lung function, physical activity, anxiolytic use, antidepressant use, smoking, diet, pulse rate, and adult social class probably mediated the association with mortality.

Adolescent-only caseness

Study members with adolescent-only caseness had a surprisingly healthy profile; for example, they were least likely to smoke or report problem drinking, and had the lowest BMI compared to all other types of affective case profile – including those who were never a case. Notably however, those with adolescent-only caseness had the highest levels of childhood sickness absence, which also attenuated the association between adolescent-only caseness and mortality, presumably acting as a confounder. In light of these observations, it was speculated that the attenuating effects of lung function, physical activity, adult social class, pulse rate, and marital status (being single) were not driven by adolescent affective symptoms, but by an underlying physical vulnerability originating in childhood. A perceived health threat can motivate an individual to undertake protective behaviours (Maddux and Rogers, 1983; Rogers, 1975), which could potentially explain the relatively healthy lifestyle associated with adolescent-only caseness.

New caseness

The results showed evidence to suggest that the relationship between new caseness and mortality was possibly due to reverse causality with poor physical health in adulthood.

Over a fifteen year follow-up, the hazard ratio for new affective caseness was most strongly attenuated by number of health conditions, smoking, and physical activity. These variables probably acted as confounders as it did not seem feasible that a single episode of affective symptoms in late-adulthood could determine lifetime patterns of smoking and physical activity, or cause chronic health conditions such diabetes, heart trouble, stroke or cancer. Antidepressant use also attenuated the association, which was likely to act as a mediator, although again could represent over-adjustment, or misclassification (see limitations, section 8.4).

8.2 Key themes

Dose-response relationship across the life course

Whilst previous literature has demonstrated a dose-response relationship between affective caseness and mortality in older persons (Geerlings et al., 2002; White et al., 2016), this is the first time an accumulation effect has been demonstrated across such a large proportion of the life course, spanning from adolescence to late-adulthood. Furthermore, the results also showed evidence that across all ages, from ages 13-15 to 53, severe affective symptoms appeared to have a long-term influence on mortality risk, compared to those who never experienced symptoms. Together, these findings suggest that every episode of severe affective symptoms (or 'case') has an important and cumulative influence on mortality risk over the life course.

Threshold effect

Notably, there was also evidence of a threshold effect whereby severe, but not moderate affective symptom accumulation appeared to increase the rate of mortality. This was likely to reflect the point at which symptoms were serious enough to interfere with daily functioning, which is in keeping with the use of cut-offs employed by clinicians for diagnosis of affective disorders (American Psychiatric Association, 2013; World Health Organization, 1992).

Explanatory pathways to mortality are dependent on affective symptom profiles

The results demonstrated that not only accumulation, but the timing and history of affective symptoms were also important. For example, the relationship between chronic caseness and mortality was likely to be mediated by poor physical health, health behaviours, psychotropic medication use, and adult social class. In contrast, there was evidence to suggest that the associations between mortality and adolescent-only and new caseness were driven by poor physical health before the onset of affective symptoms, and therefore potentially reflected reverse causality. These findings also suggested that different affective symptom profiles could have different aetiologies.

8.3 Strengths

The main strengths of this thesis reflect the rich data contained in the MRC National Survey of Health and Development (NSHD).

The NSHD is unique in having multiple measures of affective symptoms spanning from adolescence to late-adulthood; therefore this thesis was the first to examine whether the accumulation and timing of affective symptoms were important determinants of the relationship between affective symptoms and mortality over the life course. Although several previous studies have used repeated measures of depressive symptoms, all were conducted in samples of older persons, over a maximum seven-year follow-up (Geerlings et al., 2002; White et al., 2015; 2016).

Generally, existing literature has accounted poorly for potential mediating or confounding factors (Cole, 2007; Cuijpers and Smit, 2002; Wulsin et al., 1999). The NSHD contains data on a wide range of social, physiological, and behavioural measures; as a result, this thesis presents the most comprehensive overview of potential explanatory factors to date, several of which have not been previously examined. Furthermore, the use of prospective data collection techniques largely eliminated the likelihood of recall bias (with the exception of parental abuse ascertained at age 43).

Mortality was obtained for nearly all study members using NHS registry linkage data, so censoring was likely to be largely non-informative in Cox regression analyses. Very few studies of depression and mortality have included a follow-up period greater than ten years (Cole, 2007; Cuijpers and Smit, 2002; Wulsin et al., 1999); however, across all analyses,

follow-up for mortality was at least fifteen years, which allowed good insight into the role of affective symptoms over time. Maximum follow-up length was 52-years for the association between adolescent affective symptoms and mortality, which is important because survival curves for severe and no/mild symptoms only began to diverge after approximately 35 years of follow-up. Only one other study has included a follow-up approaching five decades, which was a small mixed-age sample of psychiatric patients, with only 25 deaths, and so was largely underpowered (Thomson, 2011).

The NSHD response rates have been relatively high throughout the study which has helped to minimise selection bias, in addition to the use of multiple imputation to address missing data. However, there was evidence of greater attrition among those with severe and moderate affective symptoms compared to those with no/mild symptoms. Together with the initial oversampling of those in non-manual classes and greater attrition among those who were unmarried, had lifelong limiting illness, were not in employment and who did not own their own home (Stafford et al., 2013) – this suggests that the associations between affective symptoms and mortality are, if anything, an underestimate of the effect in the general population.

8.4 Limitations

One of the main limitations is that each of the four measures of affective symptoms captured a relatively small window of time in an individual's lifespan (e.g. the GHQ-28 and PSE assess symptoms in the last four weeks and previous month, respectively), and thus were unlikely to provide an accurate assessment of affective symptom history. For example, it was shown that 8.6% of those experiencing 'new' caseness reported previous psychotropic medication use, suggesting that a considerable proportion of study members had been misclassified. Analyses relating to affective case accumulation can perhaps be interpreted with a greater level of confidence as this measure showed a strong dose-response relationship with psychotropic medication use, which acted as a crude validation. In addition, this measure attempts to capture only the frequency of affective caseness, and is therefore not dependent on timing. Other studies examining associations between affective symptom history and mortality have also relied on self-report measures capturing a short window of time (Geerlings et al., 2002; White et al., 2015; 2016) or retrospective

measures (Bruce & Leaf, 1989) subject to recall bias; which reflects the challenge in obtaining reliable measures of affective symptom history.

Psychotropic medication use was not used as a proxy for affective symptoms as it is often prescribed for conditions other than anxiety and depression (British Medical Association & Pharmaceutical Society of Great Britain, 2002), and the prevalence was too low to create accumulation measures. Methodological complications also arise with regard to whether an individual who is asymptomatic but under treatment should be treated as 'well' or 'ill'; moreover, psychotropic medication use would be conflated with help-seeking behaviour and health-service utilisation.

An additional consideration is that each measure of affective symptoms was different with respect to the mode of data collection, and the window of assessment. However, there was strong evidence to suggest that these measures captured a similar construct – for instance factor analyses showed that all four variables demonstrated a single factor solution (discussed further in section 3.4.9). It was therefore considered reasonable to combine the measures in order to assess lifetime affective caseness. Notably, strong dose-response relationships between 'affective case accumulation' and many other exposures, including psychotropic medication, also support the validity of this measure (see table 5.3.10). Whilst some studies of affective history were able to incorporate identical measures of affective symptoms (Geerlings et al., 2002; White et al., 2015; 2016), the timeframe for exposures was limited to a maximum of 7 years.

It should also be highlighted that the results relating to affective symptoms at age 13-15 and 'adolescent-only' caseness should be interpreted with a degree of caution. These analyses relied on the only measure of affective symptoms that was not self-reported, and may therefore represent a slightly different construct. Equally however, studies using the Strength and Difficulties Questionnaire to assess childhood and adolescent emotional problems have shown that teacher-rated and self-report data have similar levels of validity (Goodman, 2000).

Although the study sample was far larger than many previous studies (REF), low statistical power was a key limitation of the analyses, which meant that many estimates lacked precision, and there was inadequate power to detect small effect sizes. Furthermore, there were too few males who experienced 'chronic' caseness to establish a reliable estimate of mortality rate among this group. Likewise, it was not possible to breakdown 'intermittent'

caseness into more informative sub-categories, or to investigate explanatory pathways in the first four years of follow-up or with regard to cause-specific mortality. Nevertheless, the NSHD remains the largest long-running birth cohort study in the UK.

Inferior healthcare received by those with psychiatric disorder may strongly contribute to health inequalities between those with and without affective disorders (Mitchell et al., 2009); however factors such as non-compliance, and the quality of relationship with health care providers were not possible to measure directly using the NSHD data and so could not be examined.

8.5 Further research

Affective symptoms demonstrated a relatively consistent association with mortality at different ages across the life course, in addition to an apparent dose-response relationship. In the future, it would be interesting to examine whether these results could be replicated in other, younger cohorts, which are likely to have lower rates of smoking, in addition to greater mental health awareness. Whilst previous studies have found little evidence that the depression-mortality relationship is modified by age (Cuijpers and Smit, 2002; White et al., 2016), cohort effects are unknown. Likewise, it could be investigated whether the findings could be replicated in clinical samples, which represent a more severe group; previous work has shown that psychiatric samples have stronger associations between depression and mortality than community samples (Wulsin et al., 1999).

It would be interesting to explore whether the relationship between newly emerging affective symptoms and mortality in the first four years of follow-up holds if using a more detailed measure of lifetime affective history. It could also be examined to what extent new-onset symptoms might be driven by 'known' or 'sub-clinical' health conditions. If, for example, newly emerging symptoms were caused by underlying illness as a result of inflammatory processes, they could serve as an important early warning sign for impending health problems. Better ascertainment of affective symptom history could be achieved by reliance on medical records, or registry based data; however this would bias the sample to those with the most severe symptoms and those willing to seek help.

The relationship between adolescent-only caseness and mortality was largely unexplained which lends itself to further investigation. Since childhood sickness absence partially attenuated the association, other factors relating to childhood physical health should be examined in greater detail. Notably, even after full adjustment for all other exposures, childhood sickness absence appeared to predict mortality rates decades later, which underscores the importance of child health on later health outcomes. Equally, there were several other potential explanatory pathways that were not examined in this thesis; for instance, genetics, inflammation, and access to health care could play important explanatory roles.

The majority of previous research has focused on the relationship between depression and cancer, cardiovascular, and all-cause mortality (Chida et al., 2008; Cole and Dendukuri, 2003; Cuijpers and Smit, 2002; Hemingway and Marmot, 1999; Pinquart and Duberstein, 2010; Wulsin et al., 1999). However, the results of this thesis showed that affective caseness was most strongly associated with 'other' causes of death, although there were too few deaths to determine whether the associations were driven by a specific cause, such as digestive or respiratory diseases. This suggests that greater attention should be paid to 'other' causes of death, which could be investigated in more detail using larger cohort studies.

This was also the first study of affective symptoms and mortality to examine the role of anxiolytic use, which appeared to considerably attenuate the relationship between affective caseness and mortality, which potentially warrants further investigation. Other studies have shown that anxiolytic use is strongly associated with mortality (Parsaik et al., 2015; Weich et al., 2014), and that this relationship does not appear to be attenuated following adjustment for a range of physical health problems, psychiatric disorders (including anxiety and depression), other prescription medications, smoking and alcohol use (Weich et al., 2014). .

To better understand the role of covariates including childhood illness, physical health conditions, and anxiolytic mediation in more detail, pathway analyses or structural equation modelling could be conducted to gain further insight into potential mechanisms, such as how early-life covariates are associated with those in later-life; although these methods cannot demonstrate causality.

8.6 Policy implications

The findings of this thesis were consistent with other studies which have demonstrated considerable health inequalities between those with and without affective disorders (Chang et al., 2011; Cuijpers and Smit, 2002; Wulsin et al., 1999).

Study members who experienced chronic affective caseness had over twice the rate of mortality compared to those who were never a case. There was evidence to suggest that the relationship was largely mediated by number of health conditions, lung function, physical activity, smoking, diet, anxiolytic use, antidepressant use, pulse rate, and adult social class. Several of these factors are modifiable, which suggests that health inequalities could be reduced by providing those who experience recurrent affective symptoms with targeted support for improving health behaviours, particularly smoking cessation, healthy eating, and physical activity levels. Psychotropic medication use has been associated with numerous detrimental side effects (Hamer et al., 2011b, 2010a; Marx, 1992; Parsaik et al., 2015; Weich et al., 2014), so may potentially contribute to health problems over time. Perhaps unsurprisingly, those with chronic caseness had the highest levels of psychotropic mediation use; however this also implies that medication may not be particularly effective as a long-term treatment. Notably, those with chronic caseness had a much higher likelihood of reporting parental divorce, parental abuse, and stressful life events, compared to other type of affective case history. These findings are consistent with World Health Organization guidelines on the prevention of mental disorders, which outlines approaches to alleviate the impact of childhood stressors, including abuse and neglect, and family disruption, such as divorce. Controlled trials have demonstrated that interventions providing targeted support through either school-based or parent-focussed programmes have been successful in reducing subsequent mental health disorder (World Health Organization, 2004). Early-intervention with regard to treatment is also important as mental health problems become harder to treat if symptoms are left until they are severe. Targeted interventions teaching cognitive-behavioural coping skills to adolescents with elevated levels of depressive symptoms (but not depressive disorder), have been effective in reducing the onset and reoccurrence of depressive episodes (World Health Organization, 2004). As such, screening programmes to detect and support individuals with sub-clinical affective symptoms before they reach crisis or clinical referral could be an effective policy intervention.

In a broader context, affective disorders are becoming an increasingly large public health issue in the UK, and globally (McCrone et al., 2008; McManus et al., 2016; World Health Organization, 2015). Currently, UK government policy does not give adequate priority to mental health: despite accounting for 23% of the total burden of disease, mental health receives only 13% of NHS health expenditure (Layard, 2012). The UK Adult Psychiatric Morbidity Survey 2014 estimated that only one in three adults (37.3%) with anxiety or depressive disorders were receiving any form of treatment (McManus et al., 2016). This figure has increased sharply since the 2007 survey (24.4%) (McManus et al., 2009); however this can largely be attributed to a rise in the reported use of psychotropic medication among those with CMD symptoms, from 19.5% in 2007 to 31.6% in 2014. In contrast, there was a relatively small increase in use of psychological therapies, from 11% in 2007 to approximately 13% in 2014 (McManus et al., 2016).

The importance of early intervention was underscored by this thesis, which demonstrated an accumulation effect between affective caseness and mortality. Unfortunately, treatment access is particularly poor with respect to childhood and adolescent mental health, where there is an average wait of ten years between the first signs of becoming unwell and receiving any help (Khan, 2016). A UK Government consultation in 2009 outlined aims to 'improve the mental health and well-being of the population' through approaches such as early intervention (Department of Health, 2009); however an investigation by the charity Young Minds found more than half of councils in England had cut or frozen their budgets for child and adolescent mental health between 2010-11 and 2014-15 (Young Minds, 2015).

The persistent underinvestment in mental health appears to be a gross false economy. It is estimated that in 2016, 3.9 billion will be spent on services for anxiety and depressive disorders; yet the projected economic costs as a result of lost productivity are estimated to be close to 16 billion (McCrone et al., 2008). Moreover, these figures do not take into account the impact of affective disorders on physical illness, as highlighted in this thesis. For example, there is evidence that the presence of poor mental health alongside physical illness accounts for an additional 50% increase in the cost of healthcare. Pilot schemes have demonstrated that providing psychological support to patients with diabetes can improve health and cuts costs by 25% (NHS England, 2016). The need for an integrated mental and physical healthcare system is highlighted in the NHS report 'Five year forward view for mental health' (NHS England, 2016), which recommends ensuring that patients with severe mental health problems get access to prevention and screening programmes, such as

smoking cessation and cancer screening. Likewise, it has been suggested that Royal colleges and other bodies should work together to design curriculums which provide health professionals with a common foundation in both mental and physical health (Naylor et al., 2016).

Practically, substantial funding would be required to reduce health inequalities between those with and without affective disorders. A more cohesive approach to public health policy which invests strongly in prevention, support, and early-treatment of mental disorders, in addition to integrating mental and physical health care, would be likely to provide a more efficient and cost-effective health care system, saving money, unnecessarily suffering, and potentially lives.

8.7 Conclusion

The overall aim of this thesis was to examine the nature of the association between affective symptoms and mortality over the life course, and to investigate the role of social, behavioural, and physiological explanatory pathways.

After adjustment for sex, severe affective symptoms increased the rate of mortality at most ages across the life course, from adolescence to late-adulthood. Anxiety and depressive symptoms were equally predictive of mortality. There was evidence of an accumulation effect over the life course where the risk of mortality appeared to increase as affective caseness increased. Notably, moderate symptom accumulation did not increase the risk of mortality compared to those with no/mild symptoms, suggesting a potential threshold effect. Adolescent-only, intermittent, and chronic caseness were also associated with mortality, whilst new caseness demonstrated a strong association with mortality in the first four-years of follow-up, but not in later years, which was suggestive of revere causality with poor physical health. There was a slightly stronger relationship between affective caseness and cardiovascular mortality compared to cancer mortality; however the strongest associations appeared to be with respect to deaths from 'other' causes, particularly among those with chronic caseness.

After full adjustment, the associations between mortality and those who were a case 2 and 3-4 times (chronic caseness), and intermittent caseness were largely explained; however, associations between mortality and those who were a case at a single point in time, and adolescent-only caseness were largely unexplained. The relationship between chronic caseness and mortality was most strongly explained by number of health conditions, lung function, physical activity, smoking, diet, anxiolytic use, antidepressant use, adult social class, and pulse rate, which were thought to primarily mediate the association with mortality. In contrast, there was evidence to suggest that the relationship between mortality and adolescent-only and new caseness was driven by poor physical health. BMI, systolic blood pressure, problem drinking, social networks, stressful life events, childhood social class, or adverse-childhood experiences did not appear to be major explanatory factors.

This thesis underscores the importance of early-intervention and investment in mental health prevention in order to reduce inequalities in physical health.

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APPENDICES

Appendix A: Items relating to emotional problem from the teacher-rated behavioural questionnaires (age 13-15)

		Teacher-rated emotional problems
1	Tiredness	Do you regard this child as extremely energetic, never tired; normally energetic; always tired and "washed out"
2	Fearful	Takes a normal part in rough games; Rather frightened of rough games
3	Attention	Avoids attention; hates being in the limelight; Does not unduly avoid or seek attention
4	Fearful	As cautious as the average child 1; extremely fearful
5	Sadness	Unusually happy and contented child; generally cheerful and in good humour; usually gloomy and sad.
6	Timidity	Average—not particularly quarrelsome; a timid child.
7	Making friends	Makes friends extremely easily; Takes usual amount of time to make friends; does not seem able to make friends
8	Competitiveness	Normally competitive; diffident about competing with other children
9	Anxiety	Would you describe this child as an anxious child (i.e., apprehensive, worrying, and fearful)?; Not at all anxious; somewhat anxious; very anxious
10	Criticism	Tends to become unduly miserable or worried in reaction to criticism or punishment; Normal attitude to criticism and punishment

Appendix B: Affective items extracted from the Present-State-Examination (PSE), classified by symptoms of anxiety and depression (age 36)

	PSE items	Symptom*
1	Worrying: 'A round of painful thought which cannot be stopped and is out of proportion to the subject worried about'	Anxiety
2	Tension pains: 'band around head; pressure; tightness in scalp; ache in back of neck'	Anxiety
3	Tiredness or Exhaustion: 'Have you been getting exhausted and worn out during the day or evening even when you haven't been working very hard?	Anxiety
4	Muscular tension: 'Have you had difficulty relaxing during the past month?; muscles feel tensed up'	Anxiety
5	Restlessness: 'Have you been so fidgety or restless that you couldn't sit still?'	Anxiety
6	Nervous tension: 'Do you often feel on edge, keyed up, or mentally tense or strained?'	Anxiety
7	Autonomic anxiety: 'Have there been times lately when you have been very anxious or frightened?; did you heart beat fast? Blushing; sweating; trembling - ask for other autonomic symptoms'	Anxiety
8	Anxious foreboding: 'Have you had the feeling that something terrible might happen?'	Anxiety
9	Inefficient thinking: 'Do your thoughts tend to be muddled or slow?; can you make up your mind / make decisions about everyday matters?'	Depression
10	Poor concentration: 'Do your thoughts drift so that you don't take things in?'	Depression
11	Brooding: 'Do you tend to brood on things? So much that you even neglect your work?'	Depression
12	Loss of interest: 'Have you lost interest in work, or hobbies or recreations?'	Depression
13	Depressed mood: 'Do you keep reasonably cheerful or have you been very depressed or low-spirited recently?'	Depression
14	Hopelessness: 'How do you see the future?'	Depression
15	Self-depreciation: 'What is your opinion of yourself compared to other people?'; do you feel inferior, even worthless?'	Depression
16	Social confidence: 'How confident do you feel in yourself in talking to others, in managing with other people?'	Depression
17	Social withdrawal: 'Have you wanted to stay away from other people?'	Depression
18	Falling asleep: 'Have you had any trouble getting off to sleep during the past month?'	Anxiety
19	Anergia and retardation: 'Do you seem slowed down in your movements, or have too little energy recently?'	Depression
20	Irritability: 'Have you been very much more irritable than usual recently?'	Anxiety

*Symptom classification based on the Diagnostic and Statistical Manuals III-IV and ICD-9 definitions (American Psychiatric Association, 1994, 1980; World Health Organization, 1998) and factor analysis loadings

Appendix C: The Psychiatric Frequency Questionnaire (PSF), classified by symptoms of anxiety and depression (age 43)

	PSF items	Symptom classification*
1	Have you felt on edge or keyed up and mentally tense?	Anxiety
2	Have you been in low spirits or felt miserable?	Depression
3	Have you felt particularly low or depressed first thing in the mornings?	Depression
4	Have you had the feeling that something terrible might happen?	Anxiety
5	Have you had days when your thoughts were muddled or slow?	Depression
6	Have you had no appetite, not counting periods of physical illness	Depression
7	have you been in situations, such as a crowd or in an enclosed space or meeting people, when you became unduly anxious?	Anxiety
8	Have you been in situations when you felt shaky or sweaty or your heart pounded or you could not catch your breath?	Anxiety
9	Have you had trouble getting off to sleep?	Anxiety
10	Have you had trouble with waking up and not being able to get back to sleep?	Depression
11	Have you been frightened or worried about becoming ill or dying?	Anxiety
12	Have you felt fidgety or restless?	Anxiety
13	Have you found it hard to concentrate on things or found your thoughts drifting off to other things?	Depression
14	Have there been days when you tired out very easily?	Anxiety
15	Have there been days when you found it difficult to get things done, or had trouble getting started on things?	Depression
16	Have you had the feeling that the future does not hold much for you?	Depression
17	Have you been so caught up in your thoughts that you neglected things?	Depression
18	Have you seemed to lose interest in things?	Depression

*Symptom classification based on the Diagnostic and Statistical Manuals III-IV and ICD-9 definitions (American Psychiatric Association, 1994, 1980; World Health Organization, 1998) and factor analysis loadings

Appendix D: The 28-item General Health Questionnaire (age 53)

	GHQ-28 items	Sub-scale*
	Have you recently…	
1	Been feeling perfectly well and in good health?	A
2	Been feeling in need of a good tonic?	A
3	Been feeling run down and out of sorts?	A
4	Felt that you are ill?	A
5	Been getting pains in your head?	A
6	Been getting a feeling of tightness or pressure in your head?	A
7	Been having hot or cold spells?	A
8	Lost much sleep over worry?	B
9	Had difficulty staying asleep one you are off?	B
10	Felt constantly under strain?	B
11	Been getting edgy and bad-tempered?	B
12	Been getting scared or panicky for no good reason?	B
13	Found everything getting on top of you?	B
14	Been feeling nervous and strung-up all the time?	B
15	Been managing to keep yourself busy and occupied?	C
16	Been taking longer over the things you do?	C
17	Felt on the whole you were doing things well?	C
18	Been satisfied with the way you carried out your task?	C
19	Felt that you are playing a useful part in things?	C
20	Felt capable of making decisions about things?	C
21	Been able to enjoy your normal day-to-day activities?	C
22	Been thinking of yourself as a worthless person?	D
23	Felt that life is entirely hopeless?	D
24	Felt that life isn't worth living?	D
25	Thought of the possibility that you might make away with yourself?	D
26	Found that at times you couldn't do anything as your nerves were too bad?	D
27	Found yourself wishing you were dead and away from it all?	D
28	Found the idea of taking your life kept coming to mind?	D

***** A=Somatic symptoms; B=Anxiety and insomnia; C=Social dysfunction; D=Severe Depression

Appendix E: Cross-tabulation of affective case accumulation and affective history measures using imputed data, based on 15 imputations (n=3,001); row percentages

	%				
	Never	Adolescent only (age 13-15)	New (age 53 only)	Intermittent	Chronic
Affective caseness					
0	100	0	0	0	0
1	0	29.9	25.1	45.0	0
2	0	0	0	100	0
3-4	0	0	0	0	100

Appendix F: Descriptive characteristics of affective case accumulation by sex in the non-imputed data

	All (n=2066)		**Males** (n=1014)	**Females** (n=1052)
	n	%	%	%
Affective case				
0	1,195	57.84	66.67	49.33
1	601	29.09	25.94	32.13
2	182	8.81	5.33	12.17
3-4	88	4.26	2.07	6.37

Appendix G: Descriptive characteristics of affective case accumulation by mortality in the non-imputed and imputed data (row percentages)

		Deaths						
		Non-imputed data (n=2066)				Imputed data (n=3001)		
			All	Males (n=1014)	Females (n=1052)	All	Males (n=1492)	Females (n=1509)
	N	n	%	%	%	%	%	
Affective case								
0	1195	62	5.2	6.5	3.5	6.0	7.1	4.6
1	601	52	8.7	9.9	7.7	9.9	11.9	8.3
2	182	16	8.8	11.1	7.8	10.1	14.9	7.6
3-4	88	10	11.4	0	14.9	12.1	7.8	13.8

There is a slightly higher rate of mortality in the imputed data; although this is expected direction based on patterns of attrition and item-missingness seen in longitudinal studies (Power and Elliott, 2006; Stafford et al., 2013). There were no deaths among males who were a case 3-4 times (n=21) in the non-imputed data; note that in the imputed data the mortality risk among males who were a case 3-4 times was estimated from an additional 935 study members (and 95 deaths) that were introduced into the study sample by imputing those who were missing a single measure of affective symptoms – the outcome (mortality) was not imputed.

Appendix H: Sex adjusted associations between affective case accumulation and mortality in the non-imputed data, based on 2066 study members and 140 deaths

	Hazard ratio (95% CI) Sex adjusted
Affective case	
0	ref
1	1.77 (1.22, 2.56)*
2	1.90 (1.09, 3.31)*
3-4	2.53 (1.28, 4.97)*

*p<0.05

Appendix I: Sex adjusted associations between moderate affective symptom accumulation and mortality in the non-imputed data, based on 1195 study members and 62 deaths

	n	Hazard ratio (95% CI)
Moderate symptom case		
0	294	ref
1	405	0.61 (0.32, 1.19)
2	330	0.88 (0.46, 1.67)
3-4	133	0.82 (0.36, 1.87)

Note: The analytical sample excluded all those who ever experienced a severe case

Appendix J: Percentage of missing data by each individual variable used in the imputation model

	% imputed
Variable	
Affective symptoms, age 13-15	12.06
Affective symptoms, age 36	5.56
Affective symptoms, age 43	3.97
Affective symptoms, age 53	9.56
Sex	0.00
Social class (adult)	11.03
Education	3.67
Systolic blood pressure (mmHg)	9.76
Lung function (FEV_1)	10.73
Pulse rate (bpm)	10.26
Body mass index (kg/m^2)	9.16
Health conditions	11.76
Eating choices (ECI), age 36	30.02
Eating choices (ECI), age 43	32.66
Eating choices (ECI), age 53	46.02
Smoking history	2.87
Alcohol abuse	0.47
Exercise, age 36	4.43
Exercise, age 43	2.60
Exercise, age 53	8.20
Antidepressant use	21.69
Anxiolytic use	22.06
Marital status	8.13
Support from friends, age 43	2.83
Support from friends, age 53	8.16
Stressful life events	20.49
Social class (childhood)	3.77
Externalising, age 13-15	12.06
Childhood sickness absence	21.13
Cleanliness of child	13.40
Parental abuse	8.46
Parental divorce	5.26

Appendix K: Sex adjusted associations between affective case history and mortality in the non-imputed data, based on 2066 study members and 140 deaths

	Hazard ratio (95% CI)
Affective case history[a]	
Never	ref
Adolescent only	2.09 (1.22-3.58)*
New	1.55 (0.85-2.83)
Intermittent	1.77 (1.18-2.67)*
Chronic	2.52 (1.28-4.95)*

* p <0.05

a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); chronic = case 3-4 times

Appendix L: Descriptive characteristics of affective case history by mortality in the non-imputed and imputed data (row percentages)

	Deaths							
	Non-imputed data (n=2066)					Imputed data (n=3001)		
			All	Males (n=1014)	Females (n=1052)	All	Males (n=1492)	Females (n=1509)
	N	n	%	%	%	%	%	
Affective case history								
Never	1195	62	5.2	6.5	3.5	6.0	7.1	4.6
Adolescent only	165	17	10.3	10.4	10.2	11.4	10.8	11.9
New	172	13	7.6	9.7	6.0	9.3	11.3	7.9
Intermittent	446	38	8.5	10.1	7.6	9.6	13.8	6.9
Chronic	88	10	11.4	0	14.9	11.4	7.8	13.8

The risk of mortality is slightly higher in the imputed data compared to the non-imputed data, as discussed previously (see Appendix G).

Appendix M: Mortality from age 53 onwards by cause of death and sex in the non-imputed study sample (n=2066)

	All		**Males** (n=76)	**Females** (n=64)
Cause of death	n	%	%	%
Cancer	73	52.1	54.0	50.0
CVD	36	25.7	27.6	23.4
Other	23	16.4	11.8	21.9
Externalizing	8	5.7	6.6	4.7
Total	140	100	100	100

Appendix N: Sex adjusted sub-distribution hazard ratios for the association between affective case accumulation and cause-specific mortality in the non-imputed data (n=2066)

	SHR (95% CI)		
	Cardiovascular disease (36 deaths)	**Cancer** (73 deaths)	**Other** (23 deaths)
Affective case			
0	ref	ref	ref
1	1.49 (0.72, 3.09)	1.74 (1.06, 2.85)*	1.97 (0.68, 5.70)
2-4[a]	2.11 (0.91, 4.90)	1.26 (0.60, 2.67)	5.62 (2.12, 14.94)**

* $p < 0.05$
** $p < 0.001$
a: Those who were an affective case 2 and 3-4 times were collapsed in to a single category due to low power

Appendix O: Sex adjusted sub-distribution hazard ratios for the association between affective case history and cause-specific mortality in the non-imputed data (n=2066)

	SHR (95% CI)		
	Cardiovascular disease (36 deaths)	**Cancer** (73 deaths)	**Other** (23 deaths)
Affective case history[a]			
Never	ref	ref	ref
Adolescent only	0.89 (0.21, 3.81)	2.86 (1.51, 5.42)*	2.05 (0.44, 9.59)
New	2.21 (0.83, 5.91)	1.04 (0.41, 2.66)	1.96 (0.39, 9.89)
Intermittent	1.56 (0.70, 3.46)	1.47 (0.83, 2.62)	2.64 (0.91, 7.66)*
Chronic	2.85 (0.87, 9.33)	0.87 (0.21, 3.61)	9.58 (3.11, 29.52)**

* $p < 0.05$
** $p < 0.001$
a: Never = never a case; Adolescent only = case at age 13-15 only; New = case at age 53 only; Intermittent = case 1-2 times (not adolescent or new); chronic = case 3-4 times