Unemployment and health in the UK:

Exploring psychobiological pathways

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I, Amanda Hughes, 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 this thesis.

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ABSTRACT

Background

An extensive literature links unemployment to ill-health, but almost no research has investigated links in terms of systemic inflammation. A cardiovascular risk factor influenced by psychosocial stress, systemic inflammation may also be involved in the aetiology of depression, therefore providing a plausible pathway from the social stressor of unemployment to both psychological and physical illness. This thesis investigates associations between unemployment, systemic inflammation, and depressive symptoms in a contemporary UK context.

Methods

Cross-sectional associations of unemployment and inflammatory markers were investigated by pooling data from the Health Survey for England, Scottish Health Survey, National Child Development Survey (NCDS), and UK Household Longitudinal Survey (UKHLS) in an individual-participant meta-analysis. For longitudinal analyses, employment histories were constructed for NCDS and UKHLS participants spanning 34 and 10 years respectively. Total unemployment in months, number of spells, age at first unemployment, and recentness of last unemployment were calculated. Associations were investigated between these summary measures, inflammatory markers, and depressive symptoms by regression using multiply imputed data. Mediation was explored by socioeconomic position, health factors, health behaviours, and current unemployment.

Results

Current unemployment was robustly associated with inflammatory markers, but associations varied considerably by country (stronger outside England) and study population (no effects in UKHLS). Longitudinally, unemployment did not robustly predict inflammatory markers, and inflammatory markers did not robustly predict later depressive symptoms. Aggregated unemployment did predict

depressive symptoms, explained more by socioeconomic position and long-term illness than other factors.

Conclusions

Results suggest associations of unemployment and inflammation may be under certain conditions substantial, but are largely transitory. Country variation remains unexplained, but stronger associations in higher-unemployment areas go against a model on which the poorer health of jobseekers is primarily explained by non-causal selection effects. Results suggest the influence of inflammation in depressive aetiology is modest compared to other factors, but that unemployment may have lasting effects on psychological health.

LIST OF ABBREVIATIONS

HSE	Health Survey for England
NCDS	The National Child Development Study
SHeS	Scottish Health Survey
BHPS	British Household Panel Survey
UKHLS	The UK Household Longitudinal Study
CIS-R	Revised Clinical Interview Schedule
GHQ	General Health Questionnaire
MI	Malaise Inventory
CRP	C-reactive protein
BMI	Body Mass Index
HRT	Hormone Replacement Therapy
ILO	International Labour Organisation
NSAIDs	Non-steroidal anti-inflammatory medications
OC	Oral contraceptives
RGSC	Registrar-General's Social Classification
SEP	Socio-economic position
WHO	World Health Organization

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INTRODUCTION

Unemployment has long been linked to ill health, depression and mortality, including cardiovascular mortality. However, it is only recently that data and methods have become available which allow unresolved questions around reverse causality, bi-directional relationships, and potential pathways of effect to be addressed in novel ways using biomarkers.

The extensive literature linking unemployment to both psychological ill-health[1-3] and physical health and mortality[4, 5] increasingly suggests associations are in part causal, but to date almost no research has investigated these links in terms of systemic inflammation. An established cardiovascular risk factor influenced by psychosocial stress, there is increasing evidence that systemic inflammation may also be involved in the molecular basis of depressive symptomatology. If systemic inflammation becomes elevated in response to unemployment, and is also causally involved in depression, it would provide a plausible pathway leading from the social stressor of unemployment to psychological ill-health, as well as physical ill-health and mortality. This thesis attempts to fill a gap in the research by exploring the evidence for such a pathway, using the latest biomarker data to investigate associations between present and past unemployment, markers of systemic inflammation, and depressive symptoms in a UK context.

This thesis is structured as follows. It begins with an introduction to the concepts of unemployment, depression, and systemic inflammation, followed by a review of the current literature on associations between these three. This is followed by a methodology chapter which introduces the data sources used and discusses general methodological issues relevant to this topic. In chapter 3, the aim, objectives, and hypotheses of this thesis are stated. The first empirical chapter (Chapter 4) is a cross-sectional investigation of current unemployment and markers of systemic inflammation, to establish whether there is such an association in the following study populations: the 1958 Cohort, Health Survey for England and Scottish Health Survey, and Understanding Society. Chapter 5 extends the investigation of unemployment and markers of systemic inflammation with prospective analyses

in the 1958 Cohort and Understanding Society, to investigate whether associations persist across time. In chapter 6, results are presented of prospective analyses investigating whether markers of systemic inflammation predict later depressive symptoms in the 1958 Cohort and in Understanding Society. The aim of this chapter is to establish whether in these study populations, there is any evidence that systemic inflammation could mediate between experience of unemployment and depressive symptoms, warranting an investigation of the impact of unemployment on depression in these terms. The final empirical chapter (chapter 7) presents prospective analyses investigating associations of unemployment and depressive symptoms in the 1958 Cohort and Understanding Society. This is followed by an overall discussion chapter, in which results are summarised, emergent issues discussed, and recommendations given for further research and policy.

1 LITERATURE REVIEW

1.1 Chapter Overview

This chapter begins with an introduction to the three core concepts relevant to this thesis: unemployment, depression, and systemic inflammation. Definitions, their relevance to the life-course study of health, and measurement in large-scale surveys are briefly discussed. Following these introductions, I review the literature to date on associations between all three factors: between unemployment and depression, between unemployment and inflammation, and between inflammation and depression. In each case cross-sectional and longitudinal evidence is reviewed in turn, proposed mechanisms are discussed, and gaps in the literature identified.

1.2 Introductions: Unemployment, Depression and Inflammation

1.2.1 Unemployment

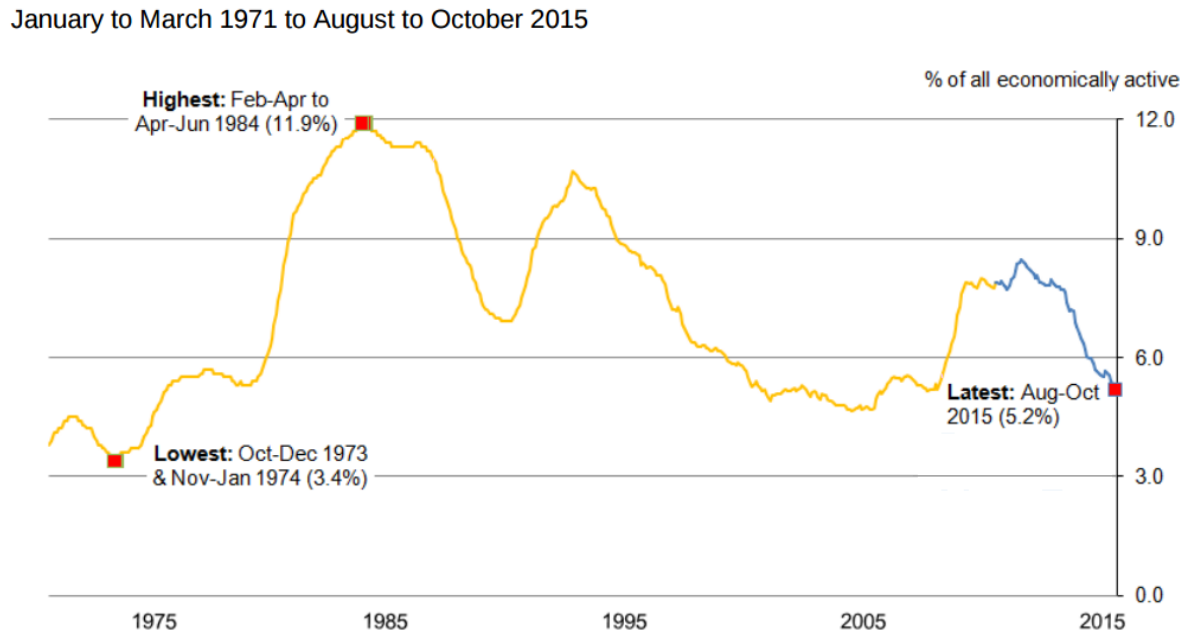
1.2.1.1 Definition and prevalence of unemployment

Unemployment is usually defined using International Labour Organization (ILO) guidelines[6], which allows cross-country comparisons[7, 8]. These define the unemployed as all those who are without work, available for work within the next two weeks, and who have sought work within the past four weeks; sometimes added to this are persons who are out of work but have found a job and are waiting to start it within two weeks[9]. Importantly, a person may fit the ILO criteria for unemployment regardless of whether they are claiming benefits. Together with those in employment or self-employment, the unemployed comprise the economically active population, defined as all persons 'who furnish the supply of labour for the production of economic goods and services'[6]. This category therefore excludes people out of the labour force due to sickness or disability, homemakers and the retired.

The UK unemployment rate (defined as the proportion of the economically active population who fit the International Labour Organization's definition of unemployed[6]) has fluctuated greatly with the

economic cycles of the past 40 years. From 3.4% in the early 1970s, unemployment rose throughout that decade and the early 1980s recession, peaking at almost 12% in 1984. It fell with recovery and rose again in the early 1990s, before entering a long-term decline. In October 2004, the unemployment rate was at 4.7% the lowest on record since 1976[10], but in 2008 began rising sharply with the onset of the economic crisis[11].

Figure 1.1: UK Unemployment Rate 1974-2015 (Source: Office for National Statistics)



UK unemployment was most recently (in December 2015, for the period August-October 2015) estimated at 5.2%, but this figure obscures important differences by age group and region. The unemployment rate is 13.6% for those aged 16-24, compared to 3.5% for those aged 35-49[12]. Regionally, it is highest in the North East at 9.8% and lowest in the South East at 3.7[13].

1.2.1.2 Unemployment and the Lifecourse

Unemployment is of particular interest to researchers in the life-course tradition because of its close links with both socioeconomic position and health across different stages of the lifecourse. Predicted by parental unemployment[14] and socioeconomic position in childhood[15], unemployment in turn affects later socioeconomic position: following unemployment, a person is at increased risk of

further unemployment in the future[16, 17] and more generally of downward social mobility, with unemployment shown to reduce income once re-employed for many years[18, 19]. At the same time, the substantial evidence for bidirectional associations between unemployment and health (reviewed in greater detail in section 1.2) and possible sensitive period effects for some outcomes [20], mean that methods using multiple time-points, and considering the age at which unemployment occurs, are especially suited to investigation of this relationship.

1.2.1.3 Measurement of unemployment

In large-scale surveys an individual's employment status is usually ascertained by self-report, with participants asked to select the best description of their current main activity from using a list of options including full-time employment, looking after home or family, unemployed, and retired[21]. This does not give a perfect measure of ILO-defined unemployment: since the description of unemployment in surveys is usually less stringent than the ILO criteria, it is likely that not all survey participants describing themselves as unemployed will, for example, be available to start work within two weeks. It is also possible that social desirability bias or financial incentives to identify differently[22] may lead to people who fit the ILO criteria of unemployed to not identify as such.

At the national level, there are two main ways to estimate prevalence of unemployment. The first involves self-reported information on employment status from surveys such as the UK's Labour Force Survey (LFS), a large sample of households nationally which began in 1973 and now provides quarterly estimations of unemployment according to the ILO definition[23]. The second approach measures unemployment using the 'claimant count' – the number of persons in receipt of unemployment benefits. Compared to estimates of ILO-defined unemployment based on survey data, this has the advantage of being available more quickly, and of giving more precise estimates of prevalence due to much larger numbers – important when looking at regional variation[22]. However, the claimant count is highly sensitive to changes in eligibility rules, making comparison of

unemployment across time (as well as countries) impossible using this measure. Since the claimant count excludes both jobseekers ineligible for unemployment-related benefits and a substantial number jobseekers not taking up benefits to which they are entitled[24], estimates of unemployment are invariably lower using the claimant count (a discrepancy visible in the latest UK estimates[9]). Hence for research into the causes and consequences of unemployment, the ILO definition is generally considered preferable because it picks up more people wanting to work[7].

1.2.2 Depression

1.2.2.1 Definitions and prevalence of depression

Unipolar depression (as distinct from much rarer bipolar disorders) is characterised by cognitive and somatic symptoms. These include persistently lowered mood and reduced capacity for enjoyment, interest and concentration, and reduction of energy and activity. Sleep is usually disturbed, appetite often diminished, and self-esteem reduced, often with feelings of guilt or worthlessness[25].

Severity of symptoms can vary greatly, even among individuals with clinically significant depression. The distinction is therefore often made between 'major' depression, for which rigorous diagnostic criteria must be fulfilled, and 'minor depression' for all other cases of clinically relevant depression[26]. But depression, in either its major or minor form, is a major public health problem globally[27]. Along with various types of anxiety disorder it is considered a 'common mental disorder' or CMD. This includes mental conditions which cause marked emotional distress and interfere with daily function, though they do not usually affect insight or cognition[28]. Compared to rarer psychotic conditions they are typically less disabling, but the greater prevalence of CMDs mean their cumulative cost to society is substantial. In a UK context, the most recent Adult Psychiatric Morbidity Survey estimated 15.1% of UK adults to be experiencing a common mental disorder, most

commonly mixed depressive/anxiety disorder[28]; the World Health Organization currently ranks depression specifically as the leading cause of disability worldwide[29].

Of enduring public health interest is the consistent finding across diverse cultures and country contexts that from adolescence onwards prevalence of depression is substantially higher for women compared to men. While attempts to definitively explain this remain contentious, it appears likely that diverse social and biological factors contribute and indeed interact[30-33].

1.2.2.2 Life events, the lifecourse, and depression

The idea that both onset and course of depressive episodes can be influenced by stressful or negative experiences is by now well established in epidemiological as well as clinical settings, and well supported by longitudinal evidence[34]. Following the work of Brown and Harris reporting the influence of childhood as well as current difficulties on chronicity of women's depressive episodes[35], and a number of studies indicating increased risk of major depression following bereavement[36], an extensive literature has investigated impact on depression of stressful or negative 'life events' (SLEs/NLEs). Generally referring to disruptions such as marital separation or divorce, violence, major personal injury or illness, or death or major illness of a close family member or spouse[37], this has also been defined operationally, for instance as any event 'which causes changes in, and demands readjustment of, an average person's normal routine'[38]. As with many of the relationships relevant to this thesis, concerns have been raised that the association between SLEs/NLEs and depression may be in part confounded, for instance if individuals genetically predisposed to depression tend to self-select into situations in which stressful life events are more probable. Nevertheless, twin studies attempting to decompose these influences support a link independent of genetic confounding[39], while studies using 'natural experiments' such exposure to natural disasters to ensure exogeneity of the event also support a causal role[40]. Recent research has therefore come to focus on more subtle questions, such as whether the influence of life events

may be different for first-onset depression compared to later episodes[34] and on possible moderators in an attempt to establish why the triggering of depressive episodes in response to similar events is not universal. Effect modification has been reported by personality factors such as neuroticism[41] as well as genetic factors, most famously by variants of the serotonin transporter gene, although this has been controversial[42, 43].

As well as specific negative events, a number of studies have indicated that more subtle effects of socioeconomic position at different stages of the lifecourse may independently affect depressive symptoms in adulthood. Disadvantaged SEP has been conceptualised by some researchers as a chronic stressor in its own right, and by others as an interactive factor which may increase vulnerability to depression following more acute life events, but in any case the evidence for independent links between SEP in childhood, adolescence, and adulthood on adult depressive symptoms is substantial[44]. Additive effects have been found whether lifecourse SEP is indexed by family poverty at different stages of childhood and adolescence[45], occupational social class in childhood and adulthood[46], or a mixture of parental and participants' own educational and occupational factors from childhood and adulthood[47]. Furthermore, such associations have been found to be robust when considering a 'health selection' pathway, whereby early health influences lifecourse SEP in a process of reverse causation[48]. Given the close links of unemployment with socioeconomic position more generally[15], this suggests similar life-course effects might be expected for repeated or long-term unemployment, or sensitive period effects of unemployment at particular life stages.

Importantly, the evidence that social factors across the lifecourse are strongly linked to later depression does not at all undermine the importance of biological factors in depressive aetiology, since depressive episodes could be influenced by distal social factors whilst also having proximate biological causes. That social and biological influences are in this sense far from mutually exclusive has been recognised, for instance, by research which hypothesises that in-utero dysregulation of the

HPA axis as a result of maternal stress can increase likelihood of depressive episodes in adulthood[44]. This thesis also takes such a view. While chapter 6 of this thesis will investigate the proximate biological cause of systemic inflammation, chapter 7 will investigate the extent to which experience of unemployment can act as a psychosocial trigger, or distal cause.

1.2.2.3 Measurement of depression in epidemiological studies

In some epidemiological studies, depressive disorders are diagnosed using structured clinical interviews[49-51] or measured by hospital admissions[52], with the effect of picking up only the most severe cases. More typically they are indexed using questionnaires designed to measure self-reported, recent symptoms of depression, with caseness defined as a score above a certain cut-off point[53]. Commonly used are the Centre for Epidemiologic Studies depression questionnaire (CES-D), the Beck Depression Inventory (BDI), and the General Health Questionnaire (GHQ). None of these screening tools are without limitations. There may be issues of comparability between the scales, for example some being weighted more towards detection of somatic symptoms, and others towards cognitive symptoms[54]. Even for extensively validated questionnaires, false positives and negatives are inevitable, and sensitivity comes at the expense of specificity[55].

1.2.3 Inflammation

1.2.3.1 The inflammatory response

Activated in response to infection, injury, or physical traumas, the inflammatory response has been described as 'a complex, highly orchestrated process involving many cell types and molecules, some of which initiate, amplify, or sustain the process, some of which attenuate it, and some of which cause it to resolve'[56]. Of central importance to the process are the cytokines. Produced by immune cells[57]and adipose tissue[58] they act as chemical messengers between immune cells[59], functioning together to regulate inflammatory and immune responses. 'Pro-inflammatory' cytokines

promote inflammatory processes, and include interleukins 1, 2, 6 and 12 (IL-1, IL-2, IL-6, IL-12), tumour necrosis factors alpha and beta (TNF-α and TNF-β), and interferon alpha (INF-α) [57]. Anti-inflammatory cytokines, such as the interleukins IL-4, IL-10 and IL-13, counteract the effects of pro-inflammatory cytokines. The balance between pro- and anti-inflammatory cytokines determines the extent of an inflammatory response[60].

In the context of infection or injury, the inflammatory response has multiple roles which ultimately contribute to bringing about a return to normal functioning. In the 'acute phase' immediately after infection or trauma, there is local release of cytokines, anaphalatoxins, and glucocorticoids[61]. Their effects are both local and systemic, setting in motion a cascade eventually resulting in increased plasma concentrations of 'acute phase' proteins[56], which can directly neutralize the inflammatory agent. These include C-reactive protein[62] and fibrinogen[63]. Secondly, the inflammatory response promotes accumulation of neutrophils and macrophages at the site of infection or trauma, where they participate in the killing of infectious agents and clearance of cellular debris. Thirdly, the acute phase proteins are involved in repair and regeneration of damaged tissue, initiating return to normal function[61].

However, an inflammatory response can also be triggered in the absence of infection or injury, typically at a lower level and for an extended period of time. Such 'systemic', 'chronic' or 'low-grade' inflammation is thought to be influenced by psychosocial stress[62, 64] and by health behaviours, in particular being positively correlated with smoking and adiposity[65, 66].

1.2.3.2 Inflammation and the stress response

It should be made clear that the inflammatory response sits in a wider network of dynamic, adaptive processes which occur centrally and peripherally and on different timescales in response a perceived threat to wellbeing[67]. When stimuli are appraised as threatening, they elicit both a psychological state that is experienced as stress, as well as a cascade of behavioural and biological adjustments – the 'stress response'[68]. In the first few seconds, activation of the sympathetic nervous system

causes release of adrenaline and noradrenaline; also activated is the hypothalamic-pituitary-adrenal (HPA) axis, a key regulatory system connecting the central nervous and endocrine systems[69]. Release of corticotropin releasing factor (CRF) from the paraventricular nucleus of the hypothalamus causes the pituitary gland to release adrenocorticotropin, which in turn induces release of glucocorticoids (cortisol for humans) from the adrenal gland[70]. These and other hormonal changes together bring about elevations in arterial pressure, heart rate and cardiac output, loss of appetite, mobilization of energy and other physiological changes: the evolved 'fight or flight' response which prepares the individual to more effectively respond to the source of danger[67]. This is of relevance to the inflammatory response due to the bidirectional communication which occurs between the endocrine and immune systems: while the pro-inflammatory cytokines act to stimulate HPA activation and subsequent elevations in plasma cortisol, cortisol suppresses the further synthesis and release of pro-inflammatory cytokines. In this way, a negative feedback loop prevents an overshoot of the inflammatory response, with intact glucocorticoid responses are crucial for keeping inflammatory responses in check [71]. However, several lines of evidence suggest that repeated activation of the stress response during chronic psychosocial stress can lead to development of glucocorticoid resistance. Animal experiments employing a social disruption paradigm to model psychosocial stress (where a group of mice among with an established social hierarchy are introduced to an intruder who challenges the hierarchy) have consistently reported development of glucocorticoid resistance during exposure, and among humans, evidence of diminished glucocorticoid sensitivity has been found for groups experiencing comparatively more stress, such as caregivers of cancer patients compared to unstressed controls [72]. Hence, one way that chronic psychosocial stress could lead to systemic inflammation is through the development of glucocorticoid resistance[72, 73].

1.2.3.3 Systemic Inflammation and health over the life-course

Systemic inflammation is considered an important cardiovascular risk factor, thought to be involved in development of atherosclerosis[62]. Thus as an index of systemic inflammation, CRP may be used as a marker for underlying disease in the form of sub-clinical atherosclerosis (although whether CRP itself is causally involved in promoting atherosclerosis is less clear[74]). Moreover CRP has been shown to predict incident myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death among healthy individuals, and to predict recurrent events and death in patients with acute or stable coronary syndromes[75, 76]. In the context of its links with both psychosocial stress and health behaviours, systemic inflammation has therefore generated considerable interest in life-course epidemiology as a possible intermediary pathway by which accumulated social conditions may influence cardiovascular health outcomes. In support of this are a number of studies showing an inverse association of aggregated life-course SEP and markers of inflammation later in life[77-79].

A related literature exists on the association of systemic inflammation and depression, with a number of researchers arguing that systemic inflammation may play a causal role in depressive symptomatology. As a focus of this thesis, the evidence for such a relationship is discussed in more depth in section 1.3.

1.2.3.4 Measurement of inflammation

Because the inflammatory response involves many different agents acting at each stage, inflammation (acute or systemic) can be indexed by serum concentrations of many 'inflammatory markers' – molecules associated with one stage or another of the cascade. Most often used are the pro-inflammatory cytokines IL-1, IL-6, TNF-α, or INF-α [57], or one of the acute phase proteins, typically C-reactive protein[62] or fibrinogen[63]. Systemic inflammation is indicated by serum CRP concentrations of 3-10mg/L, while concentrations of >10mg/L are taken to indicate current or recent infection[80]. Hence, studies investigating systemic inflammation typically exclude participants with CRP>10mg/L.

In summary, unemployment is of considerable interest to researchers because of its links with both social factors and diverse aspects of health across different stages of the lifecourse, many of which appear to be bidirectional. Depression is a leading cause of disability worldwide which appears to be influenced by specific negative life events, and also by more general socioeconomic circumstances across the lifecourse. Systemic inflammation, a temporally extended and maladaptive form of the inflammatory response to infection or injury, is influenced by psychosocial stress. An established cardiac risk factor, it may also be causally implicated in depression, and is associated with lifecourse socioeconomic position. In the remaining sections of this chapter, the evidence from previous literature is summarised linking unemployment with depression, unemployment with inflammation, and depression with inflammation.

1.3 Unemployment and depression

1.3.1 Cross-sectional associations

That unemployment is associated with elevated depressive symptoms is now well established[1-3, 81-90] but important questions remain regarding the direction of causation. Unemployment could plausibly have negative impacts on mental health mediated by poverty, psychosocial stress, or by inducing worse health behaviours[91-93]. At the same time, depression might increase chances of job loss or reduce chances of reemployment. Selection of the unhealthy into unemployment, or the healthy back into employment, would also produce cross-sectional associations between unemployment and poor health[94]. Since these processes are not mutually exclusive, the relationship between unemployment and poor health could occur in both directions in a process of reciprocal causation[95], with poor health leading to job loss leading to further deterioration in health[88]. In an effort to tease apart these processes and assess the contribution of each, studies have increasingly used longitudinal designs with adjustment for health prior to unemployment[86]. These support a link between unemployment and depression independent of selection processes[1-3, 81-86, 96]. Nevertheless, the operation of selection processes is also supported[97-100] and

intense debate continues over their extent in different working-age populations. Further questions remain regarding the nature of causal pathways. It is therefore necessary to review both causal and selection-based explanations for elevated depression among the unemployed, and the evidence in favour of each.

1.3.2 Non-causal explanations: direct selection

The 'direct selection', 'reverse causation'[3] or 'drift'[101] hypothesis holds that while unemployment does not cause poor health, poor health does causally contribute to unemployment[4, 86]. Selection may operate at two time points, increasing chances of job loss and decreasing chances of re-employment[94]. Occurrence of such effects with respect to mental health is well documented[95]. Depressive symptoms[98, 100] among employed participants have been shown to predict subsequent unemployment; other longitudinal studies support selection for lower depressive symptoms at re-employment[84, 97]. While longitudinal studies usually take account of individuals' mental health prior to job loss, it is nevertheless rarely possible to adjust for all possible confounders. Alternative methods have therefore been used to explore the extent of selection effects[92].

One approach is to study effects of job loss due to mass layoffs – the 'factory closure' method[95]. Since the cause of job loss is assumed to be exogenous to the individual, reverse causation is effectively ruled out as an explanation for subsequent ill health[102], although limitations include – with some notable exceptions[103] – typically small samples, almost always restricted to male manual workers[104]. Overall, they indicate that selection into unemployment does occur; in Paul's 2009 meta-analysis[3], associations of job loss and impaired mental health were weaker in factory closure studies compared to other studies.

Another method to gauge the extent of selection involves making comparisons between the health of the unemployed in years when the unemployment rate is high and years when it is low. In times of high unemployment job loss should be less discriminating, selection minimized, and the

unemployed more 'normal' as a result[105]. If selection is largely responsible for the ill-health of the unemployed, we should expect much smaller differences in health by employment status in these years. To some extent, this effect has been reported with respect to mortality, for instance in Finland[92], although results inconsistent with this hypothesis have been reported for Britain[105]. But in terms of mental health, this effect has been much less studied, and modification by background unemployment rate for either depression or more general mental ill-health is yet to be demonstrated. In Paul's meta-analysis, meta-regressions found a constant association of unemployment with mental ill-health over a 30-year period of rising unemployment[3]. A Finnish study comparing excess suicide mortality among the unemployed in periods of high and low unemployment found no difference according to unemployment rate[106]. One Italian study examined changes in suicide rates among the unemployed across a 12-year period of rising unemployment, and found increasing suicide rates for the unemployed, much greater than the increase in rates for the employed, during a period in which male unemployment almost doubled[107]. Insofar as suicide can be regarded as a proxy for mental ill-health, this is highly inconsistent with associations of unemployment and mental ill-health being largely caused by selection.

1.3.3 Non-causal explanations: indirect selection

The unemployment-depression association could also be partly confounded by third factors associated with both. This has been called 'indirect selection', as opposed to 'direct' selection into unemployment due to ill-health itself[15, 108]. Specifically, unemployment is itself strongly socially patterned, associated with disadvantaged social class, poverty and poor housing[109]. In a British study, likelihood of unemployment was predicted by adult occupational social class, educational attainment, social class at birth, height at age 7 (a marker for childhood conditions) and behavioural adjustment at age 11[15]. In a Swedish study, unemployment was associated with disadvantaged socioeconomic position, elementary schooling and personality factors among women, and

disadvantaged socioeconomic status, being unmarried or divorced, childlessness, and introvert personalities among men[110]. Since disadvantaged socioeconomic position is itself linked to depression [111-113] this raises the real possibility of confounding. As one study put it, many aspects of poor health among the unemployed could be due to neither causation nor direct selection, but simply reflect the social distribution of the unemployed prior to job loss[114].

These results highlight the importance of accounting for pre-unemployment socioeconomic position, and recent studies have overwhelmingly made sure to do so, using occupational social class at last employment[82], highest educational qualification[115] and/or income[81]. Associations of unemployment with depressive symptoms have been repeatedly found to be robust against such adjustment[81, 82, 97, 116-119], indicating that prior socioeconomic position cannot explain them. In any case, this is much less of a worry for longitudinal studies than for cross-sectional studies. With longitudinal or panel studies examining changes in individuals' mental health following employment transitions, it is much harder to argue that effects are driven by selection processes acting on pre-existing traits.

It has also been suggested that poor health behaviours (smoking, heavy alcohol consumption, diet and exercise) could also act as confounds if they affect both depression and unemployment independently. However, while poor health behaviours do appear associated with unemployment[110, 120, 121], the relationship is not clearly one of confounding. This will be discussed in the section on health behaviours below.

1.3.4 Causal explanations

While the non-causal processes described above undoubtedly contribute to elevated depressive symptoms among the unemployed, they do not add up to a complete explanation. Effects are still visible in studies adjusting for socioeconomic position prior to job loss, studies adjusting for mental health prior to job loss, and factory closure studies designed to minimize direct and indirect selection simultaneously. While Paul's meta-analysis found a smaller effect size for impaired mental

health among factory studies, a robust and substantial effect remained[3]. Differences in symptoms of depression and anxiety by employment status have been shown to emerge after labour market entry for young people who showed no such differences in school[96], and unemployment in British young men has been shown to pre-date symptoms of depression and anxiety resulting in medical consultation[82]. Complementing these findings is extensive evidence for the reverse process – the marked improvements in mental health frequently observed following re-employment. The three meta-analyses to date on unemployment and mental health[1-3] all reported increases in self-reported mental health following re-employment (or first employment for unemployed school-leavers) equal to or greater than decreases associated with job loss. While they also found evidence for selection at the point of reemployment[3], the apparent partial reversibility of effects following re-employment lends considerable support for causal interpretations.

What form might causal processes leading from unemployment to increased depressive symptoms take? Several processes are plausible, mediated by financial strain, psychosocial stress due to non-financial causes, health behaviour changes, and knock-on effects on other areas of life and future social position[91, 93]. In the following section, each of these pathways will be considered in turn.

1.3.4.1 Causal explanations: financial strain

Increased financial strain is perhaps the most intuitively obvious change to life circumstances following job loss, and has from the earliest studies been a focus of research into the mental health impact of unemployment. It has been repeatedly found in both US and European samples to be an important intervening factor in associations of unemployment and mental ill-health, with differences in individual economic need strongly modifying associations[84, 122-124]. In UK studies, income change since job loss and number of financial dependants has been associated with greater psychological distress during unemployment[125]; and unemployed people who had recently needed to borrow money were found to have twice as high GHQ scores as counterparts who had not, indicating greater mental distress[123]. In Sweden, unemployed participants able to claim the

more generous Income Replacement benefit suffered smaller declines in mental health during follow-up than participants with access only to the flat rate benefit[126]. This link between financial strain and mental ill-health may in turn be mediated through social isolation, since reductions in entertainment in social settings following job loss due to shortage of money is widely documented[93]. More generally, the economic resources usually provided by employment may simply be required for participation in society[124]. Financial hardship following unemployment can lead to loss of adequate accommodation, the chronic threat that this will occur, and a general sense of loss of control, all of which could plausibly impact on mental health. Strain on relationships arising from financial difficulties during unemployment may also mediate, since studies of unemployed people consistently indicate shortage of money as the greatest source of personal and family problems[93].

Consistent with substantial mediation by financial strain are comparisons across countries between which financial impact of unemployment differs. In Paul's meta-analysis of unemployment and mental ill-health, effect sizes were greater in countries with weaker unemployment protection[3]. A recent comparison of European countries by welfare state regime found comparatively poorer self-rated health among the unemployed in Anglo-Saxon states, which have the lowest wage replacement rates for the unemployed[127].

It is worth considering that if poverty following unemployment is best conceptualised as a mediator in a causal process leading to mental ill-health[116], then studies controlling for income as a marker for socioeconomic position may have over-adjusted.

1.3.4.2 Causal explanations: psychosocial stress for non-financial reasons

Research in countries where unemployment benefits are set at a high percentage of former earnings implicates additional pathways which do not operate through financial hardship. Research in

Sweden[87] and Italy[128] has found elevations in depressive symptomatology following job loss even for people receiving close to their former wage in benefits. Additional effects, mediated by psychosocial stress caused by non-financial aspects of unemployment, have been suggested as an alternative mechanism[91, 92].

To understand why unemployment could impair mental health even when financial impact is minimal, it is necessary to review the literature on the non-financial benefits of work. Of particular note is Jahoda's[129] theory that employment fulfils five 'latent' functions in addition to its manifest function of earning a living. 'First, employment imposes a time structure on the waking day; second, employment implies regularly shared experiences and contacts with people outside the nuclear family; third, employment links individuals to goals and purposes that transcend their own; fourth, employment defines aspects of personal status and identity; and finally, employment enforces activity.' For Jahoda, these non-financial benefits are crucial to mental wellbeing, and explain 'why employment is psychologically supportive even when conditions are bad, and why unemployment is psychologically destructive'[130]. Warr[93] built on Jahoda's work, adding benefits such as opportunity for skill use to develop a model of nine psychological 'vitamins' provided by employment. Stressing the importance of 'valued social position' Warr argues that in most societies being employed is undoubtedly a central source of both public and private esteem. In contrast, unemployment is associated with social stigma, and a position of lower prestige which arguably does not permit full membership of society. While provision of employment benefits may lessen the health effects caused by poverty, there may be shame attached to claiming them[93]. Consistent with this hypothesis are studies showing comparatively better mental health among the unemployed in areas where unemployment is high[131, 132], and therefore likely to be viewed as less deviant[133].

More directly, the importance of non-financial benefits of work is supported by three distinct lines of evidence. Firstly there is the qualitative research into the lived experience of unemployment, in which their absence is clearly keenly felt[93, 134-136]. Secondly, there is the literature on 'non-financial employment commitment', or 'work-role centrality'[2, 137]. This aims to quantify the extent to which individuals value employment for non-financial reasons[138, 139], and has found that large majorities of people in the US, Europe, Israel and Japan[140] would continue to work even if there were no economic reason to. Crucially, despite methodological difficulties in operationalizing the concept, individual differences in work-role centrality have been repeatedly shown to predict associations of unemployment with mental ill-health[2, 141], implicating mediation on a causal pathway.

Thirdly, there is the literature linking stressful or negative 'life events' with increased risk of depression[40]. Unemployment certainly fits the definition of an SLE as any event 'which causes changes in, and demands readjustment of, an average person's normal routine'[38] and is often regarded as such an event[142, 143], from which effects on mental health similar to other stressful life events might be expected. Some researchers have indeed conceptualized unemployment as a form of bereavement[91], characterised by a 'stage model' in which shock gives way to denial, then anxiety and distress, and finally resignation[144].

1.3.4.3 Causal explanations: knock-on effects

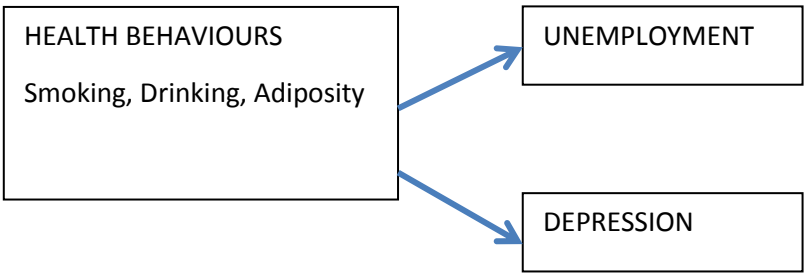
Unemployment could have indirect effects on mental health by affecting other areas of people's lives, concurrently and after re-employment. Unemployment may increase occurrence of other stressful life events with the potential for independent effects on mental health; for instance in the OPCS longitudinal study, men unemployed in 1971 were at increased risk of marital breakdown and of moving into local authority housing by 1981[145]. Additionally, unemployment may increase vulnerability of mental health to the effects of other life events[122].

As mentioned previously, there may also be lasting socioeconomic effects even after employment is regained: on risk of further unemployment in the future[16, 17] and more generally of downward social mobility, with unemployment shown to reduce income for many years[18]. Such lasting effects via future SEP may explain the scarring effects on mental health which have been observed long after an unemployment spell has ended[118]. These pathways are less relevant for explaining cross-sectional associations of unemployment and depression, but should be considered in analyses relating depression to employment history.

1.3.5 The role of health behaviours in the unemployment-depression association

The role of health behaviours (namely smoking, alcohol and adiposity) in the relationship between unemployment and depression is not clear-cut, with a least three possible interpretations. Firstly, it has been argued that health behaviours could confound associations between unemployment and depression. This argument draws on the evidence, mentioned above, that unfavourable health behaviours are associated with both[120, 121].

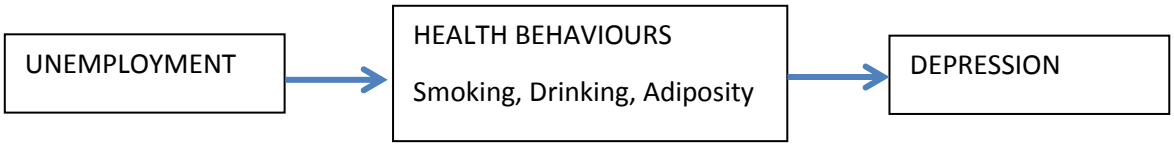
Figure 1.2: Confounding of unemployment-depression by health behaviours



However, a second view holds that it would make more sense not to conceptualise health behaviours as confounders, but rather as mediators. Level of education and personality factors are relatively stable over time and in general may precede unemployment[110]; the same cannot be said for health behaviours, which could also be plausibly affected by unemployment[143, 146]. It is

for this reason that the particular elevations in mortality by lung cancer seen among jobseekers have been interpreted by some researchers to reflect substantial mediation by health behaviours of physical health during unemployment[109]. Thus, to the extent that worsened health behaviours may in fact be links in a similar causal chain from unemployment to depression, they are best conceptualized as mediators which help explain any impact of unemployment on depression, rather than upstream factors producing confounded associations. Treating them as confounders by adjusting for them would be overadjustment, subtracting away potentially important indirect effects from estimates of the impact of unemployment on depression.

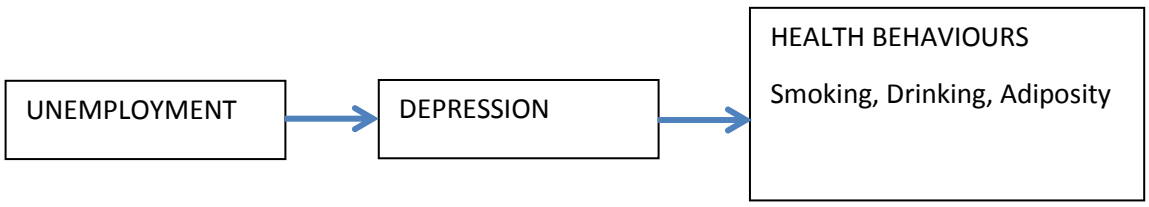
Figure 1.3: Mediation of unemployment-depression by health behaviours



It is at this point worth mentioning that one of the few studies investigating unemployment and inflammation found elevated inflammation in the unemployed to be partially mediated by health behaviours[119]. To the extent that inflammation is itself upstream of depression (another focus of this project), an indirect path via both health behaviours and inflammation may be implicated.

Meanwhile a third view, starting from an assumption that the effect of depression on health behaviours in a population is likely to be greater than the converse, holds that both these approaches are incorrect. On this interpretation, depression is best conceptualised as a potential mediator of the impact of unemployment on health behaviours, like so:

Figure 1.4: Mediation of unemployment's impact on health behaviours by depression



In this case, inclusion of health behaviours as a mediator in the relationship between unemployment and depression would again be overadjustment of a different kind. As the diagram illustrates, even in a population in which associations between depression and health behaviours is considerable, it would not make sense to treat this as a component of the association between unemployment and depression, since that is a different relationship altogether.

In order to consider which of these three models is most plausible, the previous literature on two relationships must be considered: that between unemployment and health behaviours, and that between health behaviours and depression.

1.3.5.1 Associations between unemployment and health behaviours

While it might be expected that stress associated with unemployment would lead to increased smoking, overall alcohol consumption or problem drinking, these factors must be balanced against the restriction in income which usually follows job loss, plausibly precluding substantial expenditure on alcohol and tobacco and thus reducing consumption. And while it might be expected that reduction in income following job loss could lead to weight gain via changes to diet, a reduction in sedentary behaviour due to more leisure time or active transport to reduce transport costs could have the opposite effect. Alongside any such conflicting causal processes, patterning of health behaviours by more general socioeconomic position would be expected to inflate differences in jobseekers compared to people in employment, since jobseekers are typically of a more disadvantaged SEP.

Cross-sectional studies consistently find associations between unemployment and smoking in diverse country contexts. The longitudinal evidence is mixed but appears to provide stronger support for a causal influence of unemployment on smoking than on alcohol consumption or changes in body weight, with a number of studies reporting increases in individuals' likelihood

and/or intensity of smoking following unemployment, including plant closure studies less likely to be affected by unobserved heterogeneity[147-149]. It is however worth noting analyses such as a recent German study which found that, despite cross-sectional increases in likelihood of smoking with increasing unemployment duration, in longitudinal analyses within individuals unemployment was not associated with take-up, relapse, or quitting[150]. As the authors point out, these results are better explained by a model on which pre-existing traits are independently associated with both unemployment and smoking, not a causal influence of unemployment on smoking. Meanwhile, other studies indicate that any causal influence may be highly dependent on moderating factors: a recent US study found that participants unemployed for longer than 6 months were more likely to have successfully quit smoking than their more recently unemployed counterparts, and furthermore that unemployed blue-collar workers were more successful at quitting than their white-collar counterparts[151].

As regards alcohol consumption the picture appears even more complex, reflecting the fact that alcohol consumption is not one-dimensional and can be studied in terms of total consumption, drinking pattern, and incidence/prevalence of dependency or alcohol abuse disorders. While a number studies have found evidence for an increase in alcohol consumption[152], alcohol abuse or both[153, 154] following job loss, others have reported no effect[155], a decrease in alcohol consumption[147, 156] or an increase in consumption but a decrease in symptoms of dependence[157]. A number of studies report important moderation by, for example, gender[158] local unemployment rate (with risk of problem drinking lower for jobseekers in low unemployment areas)[153] and pre-job loss alcohol consumption among individuals laid off due to business closure, with risk of increase in consumption restricted to individuals whose consumption had already been higher[159]. It is also possible that the impact of unemployment on drinking behaviour may change over time, with one study reporting an association of short-term unemployment with a reduction in consumption but longer-term unemployment with an increase[160].

The evidence for an effect of unemployment on adiposity is equally inconclusive. While a recent analysis using the British Household Panel survey reported a greater increase in self-reported weight for participants who experienced job loss than for participants who remained employed, analyses by the same authors using a different longitudinal UK dataset found this difference was restricted to women[161]. In contrast, in the UK-based 1958 Birth Cohort Study, it was found that men who had experienced the most unemployment between the ages of 16 and 33 also experienced a substantial fall in the BMI ranking in the same period[143]. An analysis of job loss in Iceland following the 2008 economic collapse similarly found that participants gained less weight after job loss than continuously employed counterparts, but significantly so only for women[162].

1.3.5.2 Associations between health behaviours and depression

1.3.5.2.1 Depression and smoking

In the case of smoking, some studies have reported an impact of depression on smoking initiation[163-165] but which does not necessarily translate into long-term smoking[166]; balanced against this are studies conversely reporting a predictive association of smoking initiation and/or status for development of depressive symptoms[167-169]. In arguing for a causal impact of smoking on depression, authors have suggested this could result from an impact of nicotine use on neurochemical systems increasing vulnerability to depression[170], or the negative impact of nicotine dependence on mental health[171]. However, against these arguments are recent Mendelian randomization studies which found no association between genetic variants linked to smoking heaviness and depression[172, 173]. A number of studies have found predictive effects of depression for smoking cessation specifically (with depressed participants less likely to successfully quit)[174-177], but it has been argued that even this latter relationship may be partly due to reverse causation, since withdrawal symptoms may increase depressive symptoms[178].

While the interaction of smoking and depression may of course be bidirectional[174, 179], it is also possible that associations between smoking and depression can in large part be explained by

confounding by socioeconomic factors, personality traits and/or genetics[180]. This is consistent with the substantial attenuation seen in many studies when these factors are taken into account[181] and suggests that past reports of causal links between depression and smoking in either direction could in part result from inadequate adjustment for confounders. Given the complexity of findings to date, some researchers have argued that the relationship between depression and smoking is best represented by a complex model with elements of both confounding and various causal processes acting in different directions between distinct elements of smoking behaviour[166, 182].

1.3.5.2.2 Depression and alcohol

While increased alcohol consumption in response to depression is intuitive as a kind of 'drinking to cope'[183], it has also been suggested that alcohol use could have depressogenic effects by inducing changes in the brain[184]. As with the literature on unemployment and alcohol, a complicated picture may reflect the mix of studies investigating differences in alcohol consumption within the recommended range, binge drinking, alcohol dependence and abuse disorders, since these cannot be assumed to have the same risk factors nor the same effects on mental health.

Some studies investigating the predictive association of Alcohol Abuse Disorder (AAD) specifically have found that it predicts onset of depressive disorders[185], including first-onset depression[186]. A longitudinal follow-up of the UK's National Psychiatric Morbidity Survey found no evidence for a predictive association of excessive drinking for incidence of depressive disorders[187], while a longitudinal Canadian study reached similar conclusions[188], and a gene variant predicting alcohol consumption was recently reported to be unassociated with current or past depression[189]. One longitudinal study reported that alcohol consumption improved depressive symptoms in the short term before worsening them[190], while another found reciprocal effects restricted to alcohol dependence, but not total consumption or binge drinking, and with the apparent increase in risk of

dependence following depressive episodes restricted to men[191]. U-shaped associations of alcohol intake and subsequent risk of incident depression have also been reported[192].

In contrast, there appears to be more evidence for the reverse relationship, i.e. that depression increases alcohol intake. Longitudinal studies have reported a predictive association between current or past depressive disorders for first-onset AAD[193], alcohol dependence[194] and heavy drinking[195]. However it has also been suggested that confounding by social factors may be at work, with the authors of one longitudinal study suggesting that associations between depression and alcohol use could be explained by more negative life events and less family support among depressed participants who drank to cope[183].

1.3.5.2.3 Depression and BMI

While it is plausible that depressive symptoms could lead to weight gain by affecting caloric intake, activity level or both, it has also been suggested that overweight and obesity could causally impact on depressive symptoms. This could be due to social processes, for instance mediated through stigma associated with overweight and its social consequences[196], or alternatively – since systemic inflammation is strongly linked to adiposity – through an inflammatory pathway[197]. However, given these rather intuitive predictions, the cross-sectional evidence for an association between overweight and obesity and depression is surprisingly inconsistent[198].

A 2008 meta-analysis of longitudinal studies[196] and a number of subsequent longitudinal studies[199-202] have found a predictive association of depression or psychological distress for weight gain or incidence of obesity. However, the meta-analysis found the relationship to be highly variable by age and gender of participants; a strong predictive association for adolescent girls contrasted with mixed results for adults, including several studies which reported a negative impact of depression on weight for older adults[196]. This inconsistency may point to simultaneous operation of contrasting processes, also supported by later studies[203] which could explain the lack of overall associations observed cross-sectionally.

On the other hand, while some longitudinal studies have found a predictive association of BMI for later depression[204], recent Mendelian randomization studies has produced conflicting results, with one supporting a causal role of high BMI in depression[205] one finding no support[206] and the other reporting an apparently protective association of a genetic risk score for high BMI against psychological distress[207]. A recent longitudinal study using the 1958 Cohort suggests an even more complex picture in which both causal directions operate for women only, and not at all points in the life-course[208]. Finally, for this relationship also there is also the possibility that confounding by sociodemographic, personality or genetic factors may explain a substantial part of observed associations[198].

In recognition of these uncertainties regarding causal directionality (firstly between unemployment and health behaviours, and secondly between health behaviours and depression), the decision was made to include the block of health behaviours in sensitivity analyses only in the investigation of the impact of unemployment on depressive symptoms. While the correct interpretation of any consequent attenuation might be unclear, this would at least allow quantification of any mediation of effects which might be occurring via health behaviours in comparison to other mediating pathways, and quantification of the association of unemployment with later depressive symptoms independent of health behaviours on the conservative interpretation that health behaviours only confound the relationship.

1.3.6 Moderation by gender and age

It has often been assumed that men should be hit worse by unemployment than women, because the alternative female role of homemaker means paid employment is of comparatively less importance for female social identity[2]. On this view, the role of homemaker during unemployment may compensate for work, providing 'latent functions' such as time structure and valued social

position, and thus mitigating the effects of unemployment on health[209]. However, comparatively little is known about whether gender actually does moderate relationships of unemployment with psychological or physical health, largely because many studies have been restricted to investigating male unemployment[1]. Effect modifications have been reported, but not always in the same direction; Paul's meta-analysis[3] found greater associations with mental ill-health for male participants, but studies of youth unemployment have found that girls were worse hit psychologically by unemployment than boys[210] It is also worth considering whether the comparative difficulty of ascertaining employment status in women may produce apparently weaker effects simply due to misclassification of exposure, if fluidity in self-definition and/or social desirability bias may cause women in search of work but also looking after a family to classify themselves as homemakers rather than unemployed, something unemployed men would not be expected to do.

Moderation by age has also been proposed. It is often assumed that psychological effects of unemployment should be less severe for people near the end of working age. They may have fewer financial commitments and family responsibilities than middle-aged unemployed, or feel under less pressure to find work if they can consider themselves 'early retired'[125]. On the other hand, effects could be worse if older jobseekers face real or perceived job discrimination, or possess outdated skills[2]. Similarly, comparatively mild psychological effects of unemployment might be expected among school-leavers, since consequences for interpersonal contact, valued social position and income reduction will typically be smaller than for middle-aged unemployed[93]. Alternatively, effects could be worse since school-leavers may feel under extra pressure to establish an identity through employment[2]. Evidence for age moderation regarding mental health is inconclusive; some studies reported worse mental health among middle-aged unemployed[125], Paul's meta-analysis found no clear pattern[3], and in McKee-Ryan's meta-analysis, associations with mental ill-health were greater in studies of school leavers than in adult samples[2].

1.3.7 Moderation by background unemployment rate

As previously mentioned, since in times and places of high unemployment job loss should be less discriminating and the unemployed more 'normal' as a result, reports of weaker associations in times and places of high unemployment have been interpreted as evidence for a substantial contribution of selection processes to associations of unemployment and poor health. This view is however controversial for a number of reasons. Firstly, this is not the only possible explanation for weaker associations in high unemployment areas. Since social stigma and disapproval of unemployment should be less harsh in areas where it more common, a high unemployment rate may buffer against effects on mental health working via loss of status or social isolation, lessening its overall impacts on mental health[131]. Secondly, it is far from clear that any effect modifications by background unemployment rate in fact occur in this direction[107], and plausible mechanisms have also been suggested for an increased impact of unemployment on psychological health in the context of high unemployment. Firstly, a high unemployment rate may increase the average length of an unemployment spell[211], with plausibly greater effects on health. Secondly, unemployment may be more distressing in areas where jobseekers perceive their prospects for re-employment as worse, regardless of actual unemployment duration[212].

In summary there is considerable evidence that unemployment is upstream of depression, although the evidence to date is inconsistent regarding modification by age, gender, background unemployment rate, and unemployment duration. The consistency of evidence for a causal link between unemployment and depressive symptoms suggests that similar associations should be expected for systemic inflammation, given the close link between inflammation and depressive symptoms. In the following sections, I review the evidence for a link between unemployment and inflammation, for a causal role of inflammation in depression, and finally for the reverse process: whether depression may have inflammatory effects.

1.4 Unemployment and Inflammation

1.4.1 Previous studies on unemployment and inflammation

The evidence for elevated inflammation during unemployment is much less extensive. Almost all research into health effects of unemployment has examined either psychological health or mortality, with a smaller literature on self-reported health. In contrast there are, to my knowledge, exactly two previous studies examining associations between unemployment and systemic inflammation.

The first was a US study by Janicki-Deverts[119] which looked at CRP levels in 1,227 black and white young men in relation to employment history. This found CRP levels were predicted by current or recent unemployment five years previously, but not 8 years previously. This was robust against adjustment for unemployment at outcome, average income across the five years before outcome measurement, age, race, BMI, and CRP 8 years before outcome measurement. Mediation analyses indicated health behaviours five years before outcome (smoking, alcohol consumption, and physical activity) accounted for 20% of the association, with aggregated depressive symptoms across the five years before outcome accounting for 6%. The authors suggest inflammatory effects of chronic psychosocial stress to account for the remainder.

The second was a Finnish study by Hintikka[213] which examined cross-sectional associations of unemployment with CRP and IL-6 in men and women of working age. Models adjusted for sex, age, marital status, economic hardship, education, smoking, alcohol consumption, common somatic diseases, Beck Depression Inventory score, and BMI. There was an age- and sex-adjusted association between continuous IL-6 and current unemployment, but this was not robust against full adjustment. No associations were found between current unemployment and continuous CRP. However, when outcome was dichotomized into 'elevated inflammatory status' – both CRP and IL-6 above the median – fully-adjusted OR for the unemployed participants was 5.2 (CI=1.55-17.43). The authors claim this is a better index of low-grade inflammation than either CRP or IL-6 individually. Again, psychosocial stress was suggested as an explanation. A major limitation was the sample size

of 225, of whom only 19 were unemployed; non-significant associations could simply result from low power.

These results raise several important issues. Firstly, Janicki-Deverts[119] investigated mediating effects of depression (CES-D score) and Hinitikka[213] adjusted for depression (BDI score) in all models. In both cases, then, there is the implicit assumption that depression is largely upstream of inflammation. But to the extent that inflammation predicts depressive symptomatology and may be causally involved in its aetiology (another focus of this project), associations between unemployment and inflammation will have been underestimated in these models. Secondly, Janicki-Deverts controlled for average income across years 10-15, while Hintikka adjusted for financial strain. If health effects of unemployment are mediated by poverty, then a major causal pathway from unemployment to ill-health was not considered. Thirdly, both studies had small sample sizes, and only one contained any women.

In summary, associations of current[213] and past[119] unemployment with elevated inflammation have now been reported, but these studies had small sample sizes and may have over-adjusted by controlling for depressive symptoms and financial strain. Associations are yet to be investigated in larger study populations, and in the UK. Mediation by depression and whether inflammatory effects of unemployment may differ by gender or age all remain to be investigated.

1.4.2 The role of health behaviours in the unemployment-inflammation association

As previously discussed in the context of associations between unemployment and depression, there is controversy over the extent to which unemployment actually leads to worsened health behaviours. However, unlike with depression, a substantial influence of health behaviours on systemic inflammation has been unequivocally established. Specifically, inflammation is strongly associated with adiposity because adipose tissue is an important source of the pro-inflammatory cytokines IL-1 and IL-6[66]; smoking is also pro-inflammatory, while alcohol intake appears to have anti-inflammatory effects[65]. Considered together with the results of Janicki-Devert's study which

supports a mediating role for health behaviours between unemployment and inflammation, this body of evidence therefore makes a much stronger case for plausible mediation by health behaviours in the association of unemployment and inflammation than in the association of unemployment and depression. For this reason, models of unemployment and inflammation in this thesis investigate the role of health behaviours a core pathway, rather than in sensitivity analyses.

1.4.3 Lifecourse influences of unemployment on systemic inflammation

While the inflammatory response to stressful demonstrated in laboratory settings and discussed in section 1.5.3 is a near-immediate one, a substantial body of animal and human research suggests that stressful experiences can influence inflammatory profiles many years later, raising the possibility that SLEs may cast a long shadow with respect to inflammation-related aspects of health. However, this has been demonstrated for the most part with respect to stressful experiences not in working-age life but during childhood [214, 215]. It has therefore been explained as biological embedding': long-lasting dysregulation of endocrine systems occurring during a period of comparative plasticity which programme pro-inflammatory tendencies into cells, in which development of resistance to the anti-inflammatory properties of cortisol (discussed in section 1.2.3.2) is implicated[68]. However, as an exposure which only becomes relevant after childhood, it does not seem likely that unemployment even early in a person's career could have a lasting effect on inflammatory profile through the same mechanisms of system dysregulation. Nonetheless, indirect effects could plausibly occur through negative impact on health behaviours linked to inflammation[143], through impact on later socioeconomic position, or, given the ambiguity of the causal directionality linking inflammation and depression, through mental health. For the purposes of this thesis, it is therefore expected that any lasting lifecourse influence of unemployment will be mediated by these factors, rather than directly accounted for by dysregulation of the inflammatory response.

1.5 Inflammation and depression

1.5.1 Cross-sectional associations

Diverse lines of evidence suggest a link between inflammatory processes and depressive symptoms and syndromes. Not only is depression strikingly comorbid with medical illnesses characterised by chronic inflammation[216], including rheumatoid arthritis[57] and coronary heart disease[217], but physically healthy individuals with major depression have been repeatedly found to display signs of activated inflammatory pathways. These include elevated concentrations of pro-inflammatory cytokines and acute phase proteins in peripheral blood compared to non-depressed individuals[60, 216, 218]. Among depressed individuals, increases in plasma concentrations of inflammatory markers have been found to correlate with severity of psychiatric disorder[57, 66]. Evidence from cross-sectional studies, and from a large body of experimental work on humans and animals, has in the last decade been summarized in several reviews[57, 59, 216, 218, 219] and meta-analyses[60, 66]. But although there is now little doubt that inflammation and depression are closely linked, the causal directionality is far from clear[60, 66].

Plenty of experimental and clinical evidence exists that depressive symptoms can be induced in animals and humans administered with pro-inflammatory treatments[218, 219]. But what this demonstrates is merely that exogenously given inflammatory agents can have depressogenic effects in specific contexts[220]. It does not follow that in populations of otherwise healthy humans, variations in naturally occurring, endogenous levels of inflammation[221] in fact play a significant role in the aetiology of depression. Due to the relative scarcity of prospective studies[66] able to investigate whether inflammation precedes depression or vice versa[220], it is unclear whether cross-sectional associations are primarily driven by depressogenic effects of inflammation, or inflammatory effects of depression. Determining which will have important implications for the treatment of both.

1.5.2 Proposed mechanisms: Inflammation to depression

An early suggestion that inflammation may be involved in the aetiology of depression came from observing side effects in hepatitis C and cancer patients treated with pro-inflammatory cytokines. Patients administered IFN-α often experience depressive symptomatology including low mood, cognitive impairment, irritability, anxiety, fatigue, apathy and loss of appetite[59], with similar effects reported after administration of IL-2 and TNF-α[57]. In animal studies, induction of behavioural changes characteristic of depression has been reported in animals injected either with pro-inflammatory cytokines, or with the bacterial endotoxin lipopolyscaccharide (LPS), which acts as a cytokine-inducer. Crucially, these changes were found to be to some extent reversible not only by anti-inflammatory agents (IL-10 or IGF-I)[219] but also by antidepressants[222]. In humans, acute increases in symptoms of depression and anxiety were found among healthy volunteers injected with LPS, and of depressed mood, fatigue, confusion, and psychomotor slowing in healthy volunteers whose immune systems were stimulated with a *Salmonella typhi* vaccine. In both cases, symptom severity correlated with cytokine concentration in peripheral blood[218].

Drawing on these findings, several models have been developed based on the idea that peripheral immune system activation, via release of pro-inflammatory cytokines, is involved in the aetiology of depression. The Inflammatory Response System model[60], macrophage theory of depression, and cytokine theory of depression[57] hold that peripheral production of cytokines acts on the brain, inducing depressive symptomatology[219].

Peripherally-produced cytokines are too large to readily penetrate the blood-brain barrier[216], but animal research suggests they can access the brain via other routes[218]. Regarding their effects within the brain, much attention has been focused on the enzyme indoleamine 2,3 dioxygenase (IDO). Activated by cytokines, IDO breaks down tryptophan, the primary precursor of serotonin. This in turn is believed to reduce serotonin availability, plausibly resulting in depressive symptomatology[57, 60]. This process also results in compounds which alter glutamatergic

neurotransmission, which may have independently depressogenic effects[60, 216]; additionally, there is evidence that cytokines could produce depressive symptoms by affecting dopamine synthesis[218].

Many behavioural changes characteristic of depression – withdrawal from social interactions, fatigue, reduced appetite, increased sleep, reduced physical activity, and reduced reactivity to reward (anhedonia) – also occur in response to infection[57, 222], and the 'sickness behaviour' model sets these behavioural changes in an evolutionary framework. Because the organism is likely to withdraw from the environment, seek rest, and reallocate energy towards fighting infection, this behavioural cluster is interpreted as an adaptive 'motivational state' analogous to hunger, thirst, or fear[218]. In contrast, depression is thought to represent a maladaptive response, brought about when activation of the immune response is exacerbated in intensity or duration[223].

1.5.3 Proposed mechanisms: depression to inflammation

Less attention has been paid to the reverse pathway – from depression to inflammation – but that depression raises risk of cardiovascular disease suggests that inflammation might mediate between the two[224]. Perturbations in depressed mood have been associated with subsequent increases of circulating IL-6[225], and both animal[226] and human studies[227, 228] have shown that production of IL-6 and other pro-inflammatory cytokines can be directly stimulated by negative emotions and psychologically stressful experiences[229]. A mediating role is implicated here for the stress systems, since depression is associated with increased sympathetic and decreased parasympathetic activity, which results in increased peripheral inflammation[66].

Interestingly, this pathway has also been discussed in terms of depression bringing about an increased *sensitization* of the inflammatory response to stressors. In other words, inflammatory effects of depression are conceptualized as interactive effects, only coming about in the presence of external stressors[221, 230]. Evidence for such an effect comes from the exaggerated inflammatory responses which depressed individuals display in response to psychologically stressful tasks[230],

and the amplified inflammatory response following childbirth observed for women with a history of major depression[231]. In the presence of everyday stressors, sensitization of the inflammatory response system could plausibly result in a chronic state of low-grade inflammation in depressed individuals[221, 230]. Again, a mediating role has been suggested for depression-induced changes to the functioning of the sympathetic nervous system, the HPA axis, or in the peripheral sensitivity of inflammatory cells to stress signals[232].

Alternatively, any inflammatory effects of depression could be largely mediated by depression-induced changes in health behaviours [221, 232]. As mentioned in the previous section, inflammation is strongly associated with adiposity because adipose tissue is an important source of the pro-inflammatory cytokines IL-1 and IL-6[66]. Hence, it is possible that depression may facilitate weight gain through sedentary behaviour, with increased adiposity in turn promoting inflammation[233]. Tobacco and alcohol consumption may also play mediating roles, since these factors are associated with both depression[221] and inflammation (physical activity and alcohol intake appear to have anti-inflammatory effects, while smoking is strongly and positively associated with inflammation)[65]. On the other hand, as already discussed, studies have been inconsistent regarding the directionality between these factors and depression, making the plausibility of an indirect path from inflammation to depression via health behaviours unclear.

It has also been suggested that the increased circulating cortisol associated with depression could influence inflammation via adiposity by promoting accumulation of triglycerides in adipocytes[221]. An additional candidate pathway goes through disturbed sleep – part of depressive symptomatology, and also associated with inflammation[232].

1.5.4 Could the association be bidirectional?

The depression-inflammation link could also result from a complex, bidirectional feedback loop[66, 220, 221] in which inflammation promotes depressive symptoms and depressive symptoms in turn promote inflammation. As Dantzer[220] puts it, 'even if inflammation develops after an episode of depression, inflammation could still promote depression by preventing recovery, promoting relapse, or enhancing functional impairment associated with later (depressive) episodes.' Several recent studies [49, 51, 221, 234-239] considered this possibility by examining both directions simultaneously. Since cross-sectional associations greatly reduce with adjustment for adiposity, a model stressing tri-directional relationships between depression, adiposity, and inflammation has also been proposed[66].

I reviewed longitudinal studies to date investigating directionality of the depression-inflammation link, published between 2003 and 2012. Twenty studies [49-52, 221, 225, 234-247] examined the inflammation to depression pathway, and seventeen [49, 51, 65, 221, 225, 229, 234-239, 245-249] examined the reverse path. Overall, these studies seem to support both causal directions, with the depression to inflammation path partly accounted for by health behaviours. Their support for each direction is summarized in Table 1.1 below; a detailed analysis of these studies is provided in Appendices A and B. As a group they are consistent with a bidirectional relationship[220], or a tri-directional model stressing adiposity[66].

Table 1.1: Summary of longitudinal studies investigating the depression-inflammation associations

Inflammation → depression (see appendix A)	**Yes**	**No**	**Unclear***	
	8 studies [240] [235] [49] [236] [50] [241] [242] [243]	10 studies [234] [239] [246] [238] [247] [221] [51] [237] [225] [52]	2 studies [244] [245]	
Depression → inflammation (see appendix B)	**Yes**	**No**	**Supports a path via health behaviours, but not a direct path**	**Unclear***
	7 studies [234] [238] [221] [51] [239] [49] [225]	4 studies [229] [235] [237] [246]	2 studies [236] [247]	4 studies [248] [65] [245] [249]

*insufficient adjustment for baseline value of outcome, or significance of the inflammatory markers used unclear

1.5.5 Confounding by health behaviours

As discussed previously in the context of links between unemployment and depression, it is possible that health behaviours (smoking, drinking and factors affecting adiposity) may influence depression. But since these factors are known to influence inflammation, this raises the possibility that health behaviours could increase both depression and inflammation independently. Studies which show substantial attenuation of the depression→inflammation association when health behaviours are taken into account and interpret the attenuation as indicating mediation[247] could therefore be alternatively interpreted as showing evidence of confounding. It is less clear that the possibility of such confounding applies to the other direction of the inflammation-depression link, since it is not obvious how outside the context of a long-term inflammatory illness, systemic inflammation could causally influence smoking, drinking, or BMI.

2 STUDY AIM, OBJECTIVES AND HYPOTHESES

As discussed in the preceding chapter, systemic inflammation could help explain repeatedly observed associations of unemployment with ill-health. However, with only two published studies to date on unemployment and inflammation, it is not known whether inflammation is typically raised among current jobseekers, nor whether any long-term 'scarring effects' on systemic inflammation remain once unemployment has ended. Meanwhile, there is substantial controversy over the extent to which systemic inflammation is causally upstream of depression. Finally, while there is an established cross-sectional association of unemployment and depressive symptoms, little is known about the extent of scarring effects on that outcome, nor how any longitudinal associations with past unemployment are best explained. This thesis aims to address each of these gaps in turn, using cross-sectional and longitudinal data sources from the UK to explore associations between current and past unemployment and markers of systemic inflammation, between past unemployment and depressive symptoms, and between earlier systemic inflammation and later depressive symptoms. All longitudinal analyses will be conducted twice, first in the 1958 Birth Cohort and then replicated in Understanding Society. Cross-sectional investigation of unemployment and inflammation will also be carried out using Health Survey for England and Scottish Health Survey data.

2.1 AIM:

This PhD will use longitudinal and cross-sectional data to examine associations between unemployment, inflammation, and depressive symptoms in UK participants of working age.

2.2 OBJECTIVE 1:

To examine cross-sectional associations between current unemployment and inflammation.

2.2.1 Hypotheses relating to objective 1:

Current unemployment will be associated with higher levels of markers indexing systemic inflammation.

2.3 OBJECTIVE 2:

To examine associations between inflammation in middle-age with the following aspects of employment history:

1. Total aggregated years spent in unemployment
2. Number of unemployment events
3. Time since last unemployment spell
4. Life period in which first unemployment occurred

2.3.1 Hypotheses relating to objective 2:

1. Inflammation at follow-up will increase with increasing total aggregated unemployment.
2. Inflammation at follow-up will increase with number of spells.
3. Inflammation will be more strongly associated with more recent unemployment.
4. Inflammation will be especially associated with unemployment spells earlier in life, indicating a sensitive period effect.

2.4 OBJECTIVE 3:

To examine whether markers of systemic inflammation predict later depressive symptoms.

2.4.1 Hypotheses relating to objective 3:

Baseline inflammatory markers will be positively associated with later depressive symptoms after controlling for depressive symptoms at baseline, supporting the cytokine theory of depression and a mediating role for systemic inflammation in the association of unemployment and depressive symptoms

2.5 OBJECTIVE 4:

To examine associations between depressive symptoms with the following aspects of employment history:

1. Current unemployment
2. Total aggregated years spent in unemployment
3. Number of unemployment events
4. Time since an unemployment spell (i.e. examining the impact of *recentness*)
5. Life period in which first unemployment occurred

2.5.1 Hypotheses relating to objective 4:

1. Number of depressive symptoms at follow-up will increase with increasing total aggregated unemployment.
2. Number of depressive symptoms at follow-up will increase with number of spells.
3. Depressive symptoms will be more strongly associated with more recent unemployment.
4. Depressive symptoms will be more strongly associated with unemployment spells early in life, indicating a sensitive period effect.

The conceptual framework is described in Figure 2.1 below, on which numbered arrows correspond to objectives 1-4.

2.6 Conceptual Framework

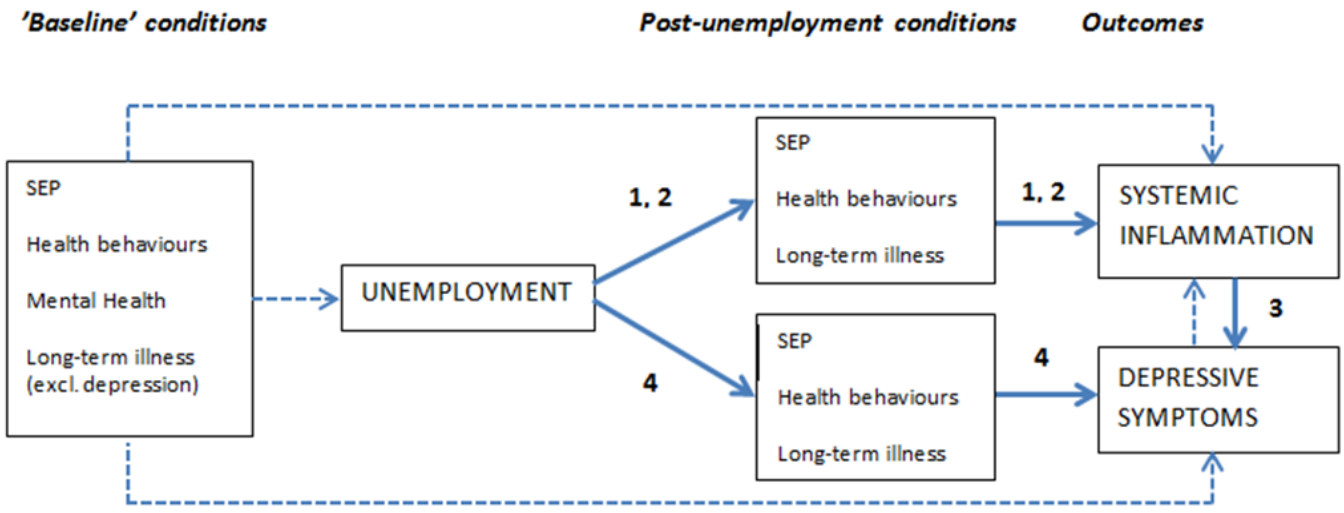


Figure 2.1: Conceptual framework based on previous literature

This conceptual model shows the pathways relating to objectives 1-4 as part of a common framework recognising that factors predating experience of unemployment must be taken into account. 'Upstream' processes are situated on the left and 'downstream' processes towards the right. Baseline factors expected on the basis of previous literature to confound associations either between unemployment and depression or inflammation, or between depressive symptoms and inflammation, are shown in the leftmost box. Then comes unemployment, followed by the box of 'post-unemployment conditions' situated between unemployment and the health outcomes: this contains those factors regarded on the basis of previous literature as likely mediators of any effect of unemployment on depressive symptoms or systemic inflammation. Throughout, solid arrows represent the associations which will be explicitly tested in this hypothesis, while the dashed arrows represent possible confounding and reverse-causation pathways considered relevant to the analytic strategy and interpretation of results; for example, the possible bidirectionality of the inflammation-depression association is recognised but the single solid arrow shows that only the inflammation-depression direction will be investigated in this thesis. It should be mentioned that the pathways to be investigated are shown together for illustrative purposes, and will be analysed independently.

A note on bidirectionality:

Given the evidence from previous research that the relationship of inflammation and depression may be bidirectional, ideally an alternative multi-staged pathway from unemployment to systemic inflammation would also be explored. This was, however, not feasible because the single measure of inflammatory markers in the available longitudinal datasets means that it would be impossible to examine change in systemic inflammation as a result of depressive symptoms.

3 DATA AND METHODS

3.1 Chapter Overview

The first section of this chapter introduces all data sources used for this thesis. Their design and structure are described, an account given of why they were chosen for particular analyses, and the measurement of the key variables used in this thesis is described. I then consider certain methodological issues concerning the longitudinal studies of unemployment, relevant to models of its effects on both inflammation and depressive symptoms, and explain the strategies chosen to deal with them. Detailed accounts of the process by which I updated the NCDS Activity Histories Dataset to take account of current activity reports from the biomedical sweep is given in Appendix C, and a complete description of how I constructed an analogous data resource for BHPS participants within UKHLS is provided in Appendix D.

3.2 INTRODUCTION TO THE DATA SOURCES

3.2.1 The National Child Development Study (NCDS) or 1958 British Birth Cohort

3.2.1.1 Rationale for using the NCDS

Three features of this study made it an especially suitable data source for the study aims. Firstly, because participants were asked detailed questions about current and past employment and non-employment at ages 16, 23, 33, 42 and 50, it contains detailed employment history data from across the life-course. Secondly, it has repeated measures of depressive symptoms at all adult sweeps which are for the most part comparable (Malaise Inventory score at ages 23, 33, 42 and 50; CIS-R at 45). Thirdly, at age 45 measurements were taken of C-reactive protein and fibrinogen, which are markers of systemic inflammation. Together with its relatively large size (N=9770 when participants were aged 50) this made it an excellent resource for investigating how current and past unemployment may impact on two parallel aspects of health, systemic inflammation and depressive symptoms, as well as the links between the latter two.

Description of the NCDS

The 1958 Birth Cohort or the National Child Development Study (NCDS) began as a study of over 17000 births in a single week in 1958.[250] Participants have since been followed up at ages 7 (sweep 1), 11 (sweep 2), 16 (sweep 3), 23(sweep 4), 33 (sweep 5), 42 (sweep 6), 45 (the biomedical sweep), 47 (sweep 7), and 50 (sweep 8). Most adult sweeps consisted of face-to-face or telephone interviews whose purpose was to collect a wide range of self-reported information on social, economic, and health-related factors. The exception was the biomedical sweep, which fell between sweeps 6 and 7 when cohort members were 44-5 years old. This involved collection by a nurse of objective measurements including height and weight, blood pressure, and blood samples for analysis. Since its purpose was to collect biological measurements, most questions about participants' social and economic circumstances were omitted.

Crucial in this project was the Activity Histories Dataset (hereafter AHD) constructed in 2011 by Maggie Hancock and colleagues. This dataset combines into a continuous narrative for each cohort member all work and non-work activities reported at sweeps 4, 5, 6, 7 and 8, resulting in employment histories spanning up to 34 years from labour market entry at 16 until age 50 (the maximum number of activities reported was 33). Both current activities and former activities occurring since the last interview could be reported. Details for each activity included activity type (a full list is provided in table 3.1 below), start month and year, end month and year, duration, and RGSC, SOC and SEG codes associated with work activities. The procedure for construction of this dataset can be found in the user guide[21].

Table 3.1: Activity Types in the Activity Histories Dataset
1 F/t paid employee 30+ hrs
2 P/t paid employee lt 30 hrs
3 F/t self-employed
4 P/t self-employed
5 Employed work but not known if ft/pt
6 Self-emp work but not know if ft/pt
7 Employed, but unpaid
8 F/t work not know if emp or s/e
9 P/t work not know if emp or s/e
10 Work but not known if ft/pt or emp/se
11 Unemployed seeking work
12 F/t education
13 Part-time education
14 Government training scheme
15 Temporarily sick/disabled
16 Permanently sick/disabled
17 Sick/ disabled not known if perm/temp
18 Looking after home/family
19 Wholly retired
20 Voluntary work
21 Maternity leave
22 Travelling/ extended holiday
97 Other

In the construction of the original Activity Histories Dataset (hereafter AHD), activity information reported at the biomedical sweep was not considered, because reports were not of comparable detail to that given at sweeps 4, 5, 6 7 and 8. Only two pieces of information concerning activities were collected at the biomedical sweep: the type of a participant's current main activity, and the date it began. No questions were asked about past activities occurring since the last sweep.

The result is that for the 9377 participants present at the biomedical sweep, two accounts exist of current activity which was supposedly current in the month of biomedical assessment - one in the AHD, from retrospective accounts given at sweep 7 or 8, and one in the biomedical data, a simple report of the participant's main current activity on the date of biomedical assessment. Merging the datasets revealed that for 13.8% of participants the two accounts did not match, with a greater discrepancy regarding unemployment. Of 132 people unemployed at the biomedical assessment

according to the AHD, only 53 reported being unemployed at the time, along with 79 others not unemployed according to the AHD.

The size of this discrepancy, reflecting the tendency for retrospectively-given information to be subject to recall error, indicated that using the Activity Histories dataset as it was could introduce substantial bias into analyses. Since half of all analysis using this dataset was investigating outcomes at the biomedical sweep, it was decided that in discrepant cases the accounts given at the time of biomedical assessment and not subject to recall error could not be ignored. I therefore decided to create an updated version of the AHD which took into account information from the biomedical sweep, using as far as possible the rules used in the initial construction of the AHD. The procedure for this is described in Appendix C.

3.2.1.2 Measurement of Inflammatory Markers in the NCDS

CRP was measured on citrated plasma by high-sensitivity nephelometric analysis of latex particles coated with CRP-monoclonal antibodies, and fibrinogen measured on citrated plasma by the Clauss method using a MDA 180 coagulometer, both at the Royal Glasgow Infirmary[251].

3.2.1.3 Measurement of Mental Health in the NCDS

Measurement of mental health has changed a number of times over successive waves of the NCDS. At age 16, which forms the baseline for longitudinal analyses involving unemployment, participants' mental health was measured using the Rutter Scale. In an effort to make this as comparable as possible with later depressive symptoms as measured by the Malaise Inventory, I followed the procedure used by Clark colleagues to adjust for early mental health in this dataset[252]. Five items were drawn from the parent version of the Rutter questionnaire indexing internalising (depression/anxiety) symptoms from which the square root of the subscale total calculated, and a further 9 items used to calculate an equivalent square root total of externalising symptoms.

For internalising symptoms, the items used describe whether, according to the parent, the child:

1. Often worries about many things
2. Tends to be on own, rather solitary
3. Often appears miserable, unhappy
4. Fearful of new situations or things
5. Fussy or over-particular

For externalising symptoms, the items used describe whether, according to the parent, the child:

1. Destroys or damages their own or other's property
2. Frequently fights, is very quarrelsome
3. Is not much liked by other children
4. Is irritable, touchy, flies off the handle
5. Is often disobedient
6. Often tells lies
7. Has stolen at least once in the past year
8. IS resentful, aggressive when corrected
9. Bullies other children

At ages 23, 33 and 42 the 24-item Malaise Inventory was used, and at 50 the shorter 9-item version. To increase comparability across the waves in these analyses, the 9-item version was drawn out of the 24-item version to measure mental health at 23, 33 and 42. The items used were therefore:

1. Whether the Cohort Member (CM) feels tired most of the time
2. Whether CM often feels miserable and depressed
3. Whether CM often gets worried about things
4. Whether CM often gets into a violent rage
5. Whether CM often suddenly scared for no good reason
6. Whether CM is easily upset or irritated
7. Whether CM is constantly keyed up and jittery
8. Whether every little thing gets on CM's nerves
9. Whether CM's heart often races like mad

At the biomedical sweep only, mental health was measured using a shortened form of the CIS-R, the Revised Clinical Interview Schedule. This version comprises sections measuring symptoms of depression, anxiety, fatigue, sleep problems, changes in appetite, forgetfulness, irritability, panic, and phobias; since it omits sections on somatic symptoms, obsession, compulsions and worries about physical health, the shortened version therefore focuses on depressive and anxiety symptoms[251]. Using the section totals (individual items for some sections were available only via special application) an overall total score can be calculated measuring psychological distress at the

biomedical sweep. Since the possible range of the shortened form was from 0-37 rather than 0-49 for the longer version CIS-R, it was not possible to define a binary measure of mental health using the standard CIS-R cut-point of 12, used in the Adult Psychiatric Morbidity Survey to estimate prevalence of common mental disorders[253]. However, since the total score was highly skewed it needed to be transformed in some way, and was therefore log-transformed for analyses.

3.2.2 The Health Survey for England (HSE) and the Scottish Health Survey (SHS)

3.2.2.1 Rationale for using the HSE & SHS

The biomedical sweep of the 1958 Cohort occurred in 2002-3, a period of extremely low unemployment in the UK, and preliminary cross-sectional analyses revealed that only 138 of 9373 participants present at the biomedical sweep were unemployed at the time of data collection. This presented serious power concerns for the analysis of cross-sectional associations with unemployment. For this reason data from the Health Survey for England (HSE) and Scottish Health Survey (SHeS) was used to study cross-sectional associations specifically. Separate years of these cross-sectional studies may be aggregated together, yielding a dataset much larger in size than the NCDS for the purposes of cross-sectional analyses.

3.2.2.2 Description of the HSE & SHS

The Health Survey for England (HSE) and the Scottish Health Survey (SHeS) are annual government surveys, each comprising a new sample each year, with core samples nationally representative of residents of private addresses[254, 255]. Each has a stratified two-stage sampling design, with households selected from primary sampling units[256]. This analysis was restricted to core-sample participants of working age, defined as 16-64 last birthday.

Surveys consisted of a face-to-face interview followed by a nurse visit during which clinical measurements were taken including serum CRP and fibrinogen, markers of systemic inflammation.

Data was aggregated from nine HSE and SHeS surveys at which CRP and fibrinogen measurements were taken for the core sample: HSE 1998, 1999, 2003, 2006 and 2009 and SHeS 2003, 2008, 2009 and 2010. At HSE 1999 and from 2008 in the SHeS only a sub-sample of core sample adults were targeted for a nurse visit, so only these participants had measurements of CRP and fibrinogen. Observations from SHeS 2011 were not used for the HSE/SHeS analysis, because introduction of a different CRP analyser resulted in measured CRP concentrations on average 15mmol/L higher, leading to concerns about consistency, but were included in the random-effects meta-analysis[257].

3.2.2.3 Measurement of Unemployment in the HSE & SHS

Current employment status could take the options described in Table 3.2. Since the HSE and SHeS did not contain any information on past activities, this information was only used for cross-sectional analyses, where categories were collapsed into employed/unemployed/sick or disabled/other economically inactive.

Table 3.2: Activity Types in HSE 1998
1 going to school or college full-time
2 in paid employment or self-employment
3 on a government scheme for employment
4 doing unpaid work for a business you own
5 waiting to take up paid work already obtained
6 looking for paid work or a government training scheme
7 intending to look for work, prevented because of temporary sickness
8 permanently unable to work, long-term sick
9 retired from paid work
10 looking after home or family
11 doing something else (specify)

3.2.2.4 Measurement of Inflammatory Markers in the HSE & SHS

In all surveys until SHeS 2010, serum CRP concentrations were analysed by the Biochemistry Department of the Royal Victoria Infirmary, Newcastle, using the N Latex CRP mono Immunoassay on the Behring Nephelometer II Analyser[258]. Imprecision at the low end of the analytical range results in a coefficient of variation of <6% for this analyser[256]. The limit of detection was 0.1mg/L.

Fibrinogen was in all surveys analysed at the Royal Victoria Infirmary Haematology Department, using a modified Clauss thrombin clotting method. The Organon Teknika MDA 180 analyser was used until HSE 2006[259-262] when the Auto Coagulation lab (TOP) CTS analyser was introduced[256, 263-266]. A correlation of 0.96 indicates results from the two analysers are comparable[266]. The limit of detection was 0.2g. Fibrinogen was not measured for participants taking drugs known to affect fibrinogen.

3.2.2.5 Measurement of depressive symptoms in the HSE & SHS

Depressive symptoms were measured by the 12-item General Health Questionnaire (GHQ). Participants were asked to respond 'not at all', 'no more than usual', 'rather more than usual', or 'much more than usual' to the following 12 questions:

1. Have you recently been able to concentrate on whatever you're doing?
2. Have you recently lost much sleep over worry?
3. Have you recently felt that you were playing a useful part in things?
4. Have you recently felt capable of making decisions about things?
5. Have you recently felt constantly under strain?
6. Have you recently felt you couldn't overcome your difficulties?
7. Have you recently been able to enjoy your normal day-to-day activities?
8. Have you recently been able to face up to problems?
9. Have you recently been feeling unhappy or depressed?
10. Have you recently been losing confidence in yourself?
11. Have you recently been thinking of yourself as a worthless person?
12. Have you recently been feeling reasonably happy, all things considered?

As is standard for this measure, Likert scoring was used to convert scores of 0-3 for 'not at all' to 'much more than usual' to a continuous 12-point score. In models requiring a binary measure, the conventional cut-off for clinically significant symptoms of 2/3 was used[267].

3.2.3 Understanding Society: The UK Household Longitudinal Study (UKHLS)

3.2.3.1 Rationale for using UKHLS

In the 1958 Birth Cohort Study, large gaps between points of information collection (up to 10 years between sweeps 4 and 5) raised concerns about the accuracy of the employment histories. This was

compounded by the high amount of discrepancy observed between activity information from the biomedical sweep and the retrospectively given reports from sweep 7 and 8 concerning that period.

In contrast, the UKHLS is an annual survey, with detailed information on current and past employment and non-employment activities collected in every wave. Such short intervals between reports should have the effect of reducing error in constructed narratives for two reasons. Firstly, recall error is minimised by the short interval. Secondly, information on start dates of current activities can be checked against reports of current activity from each previous year, making any errors which do occur easy to pick up and correct. It was for this reason that I decided to use the UKHLS in this thesis in an attempt replicate longitudinal analyses using the 1958 Birth Cohort. Substantial differences between the two datasets would suggest inaccuracies in the NCDS Activity Histories may have introduced bias. Compared to the NCDS, this data source had the disadvantage of being substantially smaller when restricted to participants with outcome measurements.

3.2.3.2 Description of the data source

The oldest component of the UKHLS began as participants of The British Household Panel Survey in 1991, as an annual survey of each adult (16+) member of a nationally representative sample of more than 5,000 households. The 1991 sample contained interviews from 10264 participants, who followed and re-interviewed annually until attrition. In subsequent years they were joined by adults currently living in new households containing the original members. Children born to original sample members joined the sample upon turning 16, and remained in the sample whether or not they still lived with an original sample member. In 1999, boost samples of households in Scotland and Wales were added[268].

In 2010, there were 12036 participants in the BHPS, of whom 3721 had been continuously present since 1991. The 12036 participants were incorporated into the second wave of the much larger UK Household Longitudinal Study (UKHLS), whose first wave had the previous year taken baseline information from 50994 new participants from 30169 new households. At each wave of the BHPS,

detailed information on both current and past work and non-work activities had been collected. This was continued in the UKHLS, such that repeated annual reports can be used together to construct detailed narratives of participants' employment history spanning as many years as they spent in the sample, across both BHPS and UKHLS years. The third wave of UKHLS included biological measurements for the BHPS component of the sample, which included concentrations of CRP and fibrinogen in blood samples.

Because so few participants at the biomedical component of wave 3 had been present since 1991 and had activity data covering all sweeps (1625), the decision was made to restrict this analysis to a ten-year study period. This resulted in 2869 participants present for the whole period from BHPS wave 11 in 2001 to the biomedical component of UKHLS Wave 3.

3.2.3.3 Measurement of current and past unemployment

At each annual wave of the BHPS and UKHLS, information was collected on current and up to 10 past activities in the past year, which could be of the following types:

Table 3.3: Activity Types at BHPS Wave 1 (1991)
1 self-employed
2 employed
3 unemployed
4 retired
5 maternity leave
6 family care
7 ft study, school
8 lt sick, disabled
9 govt training scheme
10 other

This information was used both to classify current unemployment status and to construct activity histories for every participant ever in the BHPS or UKHLS for as long as they were in the study, the procedure for which is described in detail in Appendix D.

3.2.3.4 Measurement of Inflammatory Markers

CRP and fibrinogen were analysed by Newcastle upon Tyne Hospitals NHS Foundation Trust on a Roche machine; the limits of detection were 0.2 mg/L for CRP and 0.5g/L for fibrinogen[269].

3.2.3.5 Measurement of depressive symptoms

In the BHPS and UKHLS, depressive symptoms were measured using the GHQ-12, whose individual items are described above on page 60. Again, Likert scoring was used to convert scores of 0,1,2 or 3 for each item to a single continuous score whose cut-off for clinically significant symptoms in 2.

3.3 GENERAL ISSUES IN THE LONGITUDINAL STUDY OF UNEMPLOYMENT

Chapters 6 and 7 of this thesis report on investigations of how unemployment over a number of years may affect later health, using two separate data sources and measured by two distinct outcomes: depressive symptoms and systemic inflammation. Aspects of the analytical approach taken and the covariates chosen differ according to outcome and dataset, due to both theoretical and practical considerations. For instance, the age distribution of the datasets is different, meaning that appropriate age groupings will differ between them. Similarly, certain medications would be expected to affect systemic inflammation but not depressive symptoms, so would need to be taken into account in some analyses but not others. Such differences are discussed in more detail in the introduction to the individual analyses. However, much of the methodological issues apply equally to analyses of both outcomes and across both datasets. These general issues in the longitudinal study of unemployment are discussed below.

3.3.1 When to measure socioeconomic position

As discussed in the introduction, the fact that socioeconomic position strongly predicts health outcomes, but likelihood of unemployment itself is strongly socially patterned, means adjustment

for prior SEP is essential in any study of health effects of unemployment. Failure to do so is likely to inflate estimates of impacts of unemployment itself.

At the same time, the evidence that socioeconomic position may itself be influenced by prior experience of unemployment[18] suggests long-term impacts of unemployment on health may be partly mediated by impaired upward social mobility or downward social mobility. Insofar as this occurs, adjusting for socioeconomic position at outcome measurement would discount valid indirect effects working over the life-course via SEP even when employed.

In an attempt to balance these concerns, in all longitudinal models I included socioeconomic position at two time-points: baseline and outcome measurement. In the 1958 Cohort Study baseline SEP was defined as parental SEP at age 16, indexed by participants' parents' housing tenure and occupational social class of the participant's father. Since this is when the employment histories begin, SEP at this point has the advantage of being unaffected by any prior unemployment. In the BHPS, not all participants were present in the sample until well after labour market entry, so models instead adjusted for SEP at the start of the 10-year follow-up period, defined by participants' own housing tenure and occupational social class (RGSC) from current or most recent employment. SEP at outcome measurement – always in adulthood but differing according to the analysis and data source – was indexed by participants' own housing tenure and RGSC from current or most recent employment. This two-fold approach to SEP meant that in longitudinal models, SEP at labour market entry could be consistently included as a potential confounder but SEP at outcome could be separately explored as a possible mediator.

3.3.2 Long-term physical illness

Similar concerns exist with long-term illness/disability. While chronic health conditions are likely to increase likelihood of unemployment, they are also strongly linked to both depressive symptoms and systemic inflammation, raising the possibility of confounding. However, to the extent that unemployment might causally impact on physical health, this could in turn affect both mental health

and markers of systemic inflammation - thus acting as a mediator in an indirect pathway. Again I have attempted to balance these concerns by including, where possible, independent measures of both mental and physical health at both labour market entry and outcome measurement.

3.3.3 Lifetime measures of unemployment

There are many ways unemployment over the life-course could be operationalised. Informed by the literature of 'accumulation' of social exposures, it would make sense to study the effects of total aggregated unemployment in months or years during follow-up, as previous studies have done[118]. However, informed by the stressful life events literature, a conceptualization stressing the number of events (rather than their total duration) would be suggested. Informed by the idea of 'sensitive periods' and the economic literature suggesting that early labour market disadvantage in particular can have lasting effects on SEP as well as health[270], it would make sense to investigate associations of later health with the age of first unemployment. Finally, since it is unclear how long any health effects of unemployment last once employment is regained, it would make sense to investigate associations with time since most recent unemployment.

A further subtlety is that these distinct measures of unemployment are likely to confound one another, due to the fact that unemployment tends to cluster longitudinally within individuals. For example, a person who experienced unemployment in their early twenties is more likely to accumulate further unemployment in later years. If years later an association is observed between youth unemployment and depression in midlife, this could be a direct 'scarring' effect of youth unemployment, indicating a sensitive period effect. However, an alternative explanation would involve accumulation effects, since the people who experienced youth unemployment will likely be those who will have accumulated the most years of unemployment by midlife, even if no periods are particularly sensitive. Similarly, an especially strong association of depressive symptoms with recent unemployment could indicate strong effects of unemployment on psychological health which are nevertheless temporary, but could also point to scarring or accumulation effects since participants

who have been recently unemployed in midlife will have likely experienced more unemployment earlier in the life-course than participants with no recent unemployment.

I therefore opted to operationalise past unemployment in five ways. Accumulation effects were investigated in two ways, using total aggregated unemployment in years over the study period, and total number of unemployment spells over the study period.

Timing of first unemployment was examined in two ways. Firstly, analysis was restricted to people who would never be unemployed again, which would isolate any direct scarring effects resulting from exposure during sensitive periods. Secondly, this was examined including people who would experience further unemployment, allowing an indirect path via later unemployment to be investigated.

Finally, recentness of last unemployment was restricted to people who had only been unemployed once, such that their last unemployment was also their first unemployment. This was necessary to decouple recentness of last unemployment from accumulation effects resulting from other spells earlier in life.

Since in the UKHLS and HSE/SHeS participants' employment histories prior to study entry are unknown, it could not be determined whether participants had never been unemployed prior to a particular spell. Analyses investigating effects of first and most recent unemployment could therefore only be investigated using the 1958 Cohort Study.

3.3.4 Current employment status at outcome

Some previous analyses attempting to quantify long-term effects of past unemployment adjust for current employment status[119], while others do not[118]. This variation reflects a further subtlety to this topic. On the one hand, there is extensive evidence for cross-sectional associations between unemployment and poor health, which one might wish to control for in the study of 'scarring' effects of past unemployment. On the other hand, long-term effects of unemployment on health may work

in part through increased chance of further unemployment at every point in the future. If this is the case, adjustment for employment status at outcome would discount a valid indirect pathway from past unemployment to impaired health. As with physical health and socioeconomic position, my solution was again to conceptualise employment status at the point of outcome measurement as a potential mediator in all longitudinal analyses. The summary measures of lifetime unemployment were therefore calculated to include unemployment spells current at the time of outcome measurement, but in additional models current unemployment was controlled for and the impact on effect sizes observed.

3.3.5 Baseline measurement of the outcome

In any analysis where reverse causation is a concern, adjustment for baseline value of the outcome is necessary to isolate one causal direction from the other. To this end, a baseline measure of depressive symptoms was included in all analyses of depressive symptoms. In analyses using UKHLS, GHQ score at the start of the ten-year period was included as a baseline measure, with depressive symptoms at outcome also measured by the GHQ. In analyses using NCDS data it was not possible to use the same measure depressive symptoms at baseline and outcome, because different sweeps of the study used scales to investigate psychological health. While depressive symptoms were indexed by the Malaise Inventory when participants were aged 23, 33, and 50, this scale was not used at age 16 when participants' employment histories begin. I therefore used a procedure developed by Clark and colleagues[252] to draw out a comparable measure of depressive/anxiety or 'internalizing' symptoms, and a measure of externalizing symptoms, using a subscale of the Rutter Scale used at 16. This procedure has previously been used in this dataset to adjust for early depressive/anxiety symptoms in the study of later mental health. Since this is not a perfectly comparable measure, in sensitivity analyses we examined whether externalising symptoms could also confound later associations of MI score and unemployment in midlife.

For analyses where the outcome was systemic inflammation, adjustment for baseline value of the outcome as such was not possible, since in both the NCDS and UKHLS systemic inflammation has only been measured once. While this is clearly not ideal, reverse causation – strictly defined – is less of a concern with systemic inflammation than depressive symptoms. The health conditions for which chronic inflammation is a risk factor may certainly affect chance of job loss or reemployment; however, as an intermediary 'sub-clinical' state, low-grade inflammation itself is on its own unlikely to do so. For these analyses it was therefore crucial instead to adequately control for any health conditions associated with systemic inflammation which may also influence chance of job loss or reemployment. Hence in all analyses of systemic inflammation, depressive symptoms were controlled for in addition to physical illnesses.

3.3.6 Education

In analyses of outcomes at age 50 using the 1958 Cohort, socioeconomic position is often indexed by highest educational qualification by this age[118]. However, since this includes recently gained qualifications, it is an index of socioeconomic position at age 50; as discussed previously, this is not a measure of initial conditions and may adjust away indirect effects. Nevertheless, it does raise an important question: should education be adjusted for in the study of associations of unemployment and health, as part of the initial conditions at labour market entry?

While variables such as occupational housing tenure and social class might be expected to better index material circumstances, some researchers argue that education could impact on health outcomes over and above other dimensions of socioeconomic position, for instance by making people more responsive to health education messages [271]. However, adjusting for education at labour market entry raises its own problems, because age of labour market entry itself depends on years spent in education. Since it is impossible to have a main activity of 'unemployed, seeking work' for more than a few months per year whilst in full-time education, the possibility for a person to experience a substantial amount of unemployment when aged 16-21 is effectively removed by

staying in education through these years. If more educated participants are expected to end up with less accumulated unemployment by midlife, and will definitely avoid unemployment during what may be a sensitive period, then apparently beneficial effects of education and negative effects of unemployment then become very difficult to distinguish by adjustment.

A second, related difficulty stems from the fact that educational qualifications tend to make people more employable, and thus make future unemployment less likely. Thus, insofar as education affects health via unemployment, adjusting for educational qualifications would clearly be overadjustment. While this criticism could also be directed at other dimensions of SEP, it is arguable that dimensions of SEP more closely related to material conditions should be expected to exert less of their effects via unemployment than education. Indeed, much of the literature on the effects of education on health focuses on job type, which has already been adjusted for.

A third concern results from the mixed age composition of both the HSE/SHeS and the BHPS/UKHLS samples. Unlike with the 1958 Cohort, highest educational attainment would mean something quite different for participants who had left school at different times in the 20th or early 21st century.

As a result of these concerns, the decision was made not to adjust for education in addition to housing tenure and occupational social class in any of the study populations. However, in the 1958 Cohort study, where as a result of the identical age of participants the meaning of a given educational qualification should not vary between participants due to historical shifts, sensitivity analyses were employed restricting participants to 1) those who left school at 16 and b) those who stayed in education through university, with models looking at effects of unemployment re-run within each of these subgroups.

3.4 PREVIEW

In the following four chapters, results are presented of analyses using the data sources described in sections 1-3 of this chapter and according to the principles described in section 4 of this chapter, to investigate associations between unemployment, inflammation and depressive symptoms as

described in objectives 1-4. This begins in the next chapter with cross-sectional analyses relating to objective 1: an investigation of associations between current unemployment and markers of systemic inflammation.

4 UNEMPLOYMENT AND INFLAMMATION, CROSS-SECTIONAL ANALYSES

4.1 Chapter Overview

This chapter presents results of analyses relating to objective 1: the investigation of cross-sectional associations between current unemployment and markers of systemic inflammation. It was hypothesised that current unemployment will be associated with higher levels of inflammatory markers. After a discussion of shared methods, specific methods and results are presented and discussed for the three individual replications of this analysis (in the 1958 Cohort Study, Health Survey for England/Scottish Health Survey, and Understanding Society). In the following section, methods and results are presented and discussed of a pooled meta-analysis across all study populations, which is then followed by an overall discussion of all analyses relating to objective 1.

4.2 Methods relating to all datasets

4.2.1 Measures (all datasets)

Not all relevant factors were measured in a consistent way across all surveys. As a result, slightly different categorizations of long-term illness and alcohol consumption, and more than one measure of mental health, was employed across the individual analyses, but subsequently harmonised for meta-analytic models. While the specific measurement of these factors is described for each dataset in turn along with the sensitivity analyses possible for each individual study, the categorization of factors which were measured consistently is described below.

4.2.1.1 Employment status

In all analyses unemployment was defined using the International Labour Organization definition, on which participants were considered unemployed if they were without work and seeking work, or waiting to take up work[6]. The reference group in all analyses was participants in paid employment or self-employment. Participants who were firstly out of the labour force due to sickness/disability, and secondly otherwise economically inactive (including homemakers, the retired, full-time

students, participants in government training or doing unpaid work) were analysed separately as a third and fourth group. Participants who were unemployed but temporarily prevented from seeking work due to illness were included with the sick/disabled group.

4.2.1.2 Systemic Inflammation

In all datasets, systemic inflammation was indexed by C-reactive protein (CRP) in mg/L and fibrinogen in g/L; these were both log-transformed due to positively skewed distribution. A third set of models investigated odds of raised CRP defined as >3mg/L, the standard cut-off in CRP analyses in recognition of the clinically significant increase in cardiovascular risk past this point[272]. Information on processing of the samples in each study is included in the data and methods chapter.

Socioeconomic position

In all analyses, two dimensions of socioeconomic position were included as covariates. Occupational social class from current or most recent employment was classified using the 6-group Registrar General's Social Classification (professional/managerial/skilled non-manual/skilled manual/semi-skilled/unskilled occupations). Housing tenure was classified as owns home outright, buying with a mortgage/loan, renting (from council or housing association) and private renting/other.

Health behaviours

In all analyses, smoking was categorised as never smoker, ex-smoker, current (up to 10/day), current (11-20/day) and current (>20/day). Height and weight were in every study assessed by a nurse, from which BMI was calculated and categorised into WHO BMI categories (<18.5, 18.5-24.99, 25.0-29.99, 30-34.99, ≥35) and used as measure of adiposity.

Analysis (all datasets)

All analyses were restricted to participants of working age at the time of blood sample collection, which meant exclusion of participants aged <16 or >64 from HSE, SHeS and UKHLS samples.

For all studies, multivariate linear regression was used to examine associations of unemployment with serum concentrations of log-transformed CRP and fibrinogen, and multivariate logistic regression to investigate associations of unemployment with odds of CRP>3mg/L.

Crude models adjusted for age, sex and country only, and successive models additionally adjusted for SEP (RGSC and housing tenure), presence of a long-term illness, health behaviours (smoking, alcohol consumption and categorized BMI), and finally symptoms of depression/anxiety.

Interactions by gender were considered, since studies have indicated associations of unemployment with ill-health may be greater for men[3]. An age interaction was considered in study populations where age varied, since studies have indicated associations of unemployment with ill-health may be greater for younger people[5]. Samples were for this purpose split into three equal-width age bands, corresponding to early career (16-31), mid-career (32-47) and late-career (48-64) participants. Within each band, age in years was adjusted for.

4.2.1.3 Sensitivity analyses

Since all analyses were complete-case, crude models (sex, age, country) for all studies were run with an interaction term against a marker for whether participants were lacking further covariates, to see if their exclusion could have produced bias. For NCDS and UKHLS samples, the impact of considering the time of day, season and processing time of blood samples was also examined (this information was not available for all HSE/SHeS surveys). Finally, fully-adjusted models were re-run excluding participants taking medications which could affect inflammation or fibrinogen specifically. For NCDS and UKHLS samples, this included hormone replacement therapy and oral contraceptives (not available for all HSE/SHeS surveys).

There were concerns that results may have been affected by changing composition of the employed baseline group over the study period, due to a rise in part-time, precarious, and self-employment since the last recession. An additional sensitivity analysis in the UKHLS data therefore explored the

impact of defining the baseline group more narrowly, by treating part-time workers and self-employed participants as separate groups.

4.3 Analyses using NCDS

4.3.1 Methods

4.3.1.1 Participants

Analysis began using all participants present at the 2003 biomedical sweep when blood samples were taken (N=9377), from which participants lacking CRP measurements (N=1685) or fibrinogen measurements (N=1694) were excluded from CRP and fibrinogen analyses respectively. A further 416 participants were excluded for missing employment status or covariates. Remaining participants with CRP>10mg/L were removed from both CRP and fibrinogen analyses (N=207, N=206), since this is considered evidence of current infection, rather than chronic processes[80].

4.3.1.2 Measures

As described in the Methods Chapter, employment status was derived firstly from accounts of current employment status reported at the biomedical sweep; only where this was missing were retrospectively-given accounts from sweep 7 or 8 used.

Frequency of alcohol consumption was reported at sweep 6, approximately two years prior to measurement of inflammatory markers. This was categorised as 4+days/week, 2-3 days/week, 2-3/month-1/week, less often, or not in last 12 months/non-drinker.

Long-term illness (mental or physical) was included as a binary measure since no information was available on whether illness was limiting. Depressive/anxiety symptoms were indexed by total CIS-R score at the biomedical sweep; this was highly skewed and therefore log-transformed. Non-steroidal anti-inflammatory drugs, systemic corticosteroids, corticosteroid injections, lipid-lowering drugs, beta-blockers, fibrates, aspirin and ibuprofen, hormone replacement therapy, and oral contraceptives were classified as medications that could influence inflammatory marker levels.

4.3.1.3 Analysis

The NCDS does not have a complex sample design, so it was not necessary to take account of clustering by PSU or strata. The lack of weights at the biomedical sweep meant it was not possible to weight the sample for non-response.

Table 4.1: Descriptive Characteristics of the sample (NCDS)

		Initial sample (present at biomedical sweep) N=9377	Final analytic sample for CRP N=7027	Final analytic sample for fibrinogen N=7019
		%	%	%
Gender	Men	49.8	50.4	50.3
	Women	50.3	49.6	49.7
		Mean(SD)	Mean(SD)	Mean(SD)
Inflammatory markers	C-reactive protein*	2.18(4.28)	1.64(1.84)	-
	Fibrinogen**	2.96(0.62)	-	2.91(0.57)
		%	%	%
Occupational social class (RGSC) from current or past employment	i –professional	5.1	5.4	5.4
	ii-managerial-technical	35.1	37.0	37.0
	iii-nm - skilled non-manual	21.2	21.3	21.3
	iii-m - skilled manual	18.7	19.9	19.8
	iv - semi-skilled manual	12.8	12.9	12.9
	v – unskilled manual	3.5	3.6	3.6
	Missing	3.6		
Housing tenure	Owns outright	7.9	8.0	8.0
	Buying with a mortgage/loan	72.1	76.3	76.3
	Council/LHA rented	10.0	9.4	9.4
	Private rented/other	6.5	6.3	6.3
	Missing	3.5		
Economic status	In paid employment	87.3	89.3	89.2
	Unemployed, seeking work	1.5	1.4	1.4
	Sick or disabled	4.5	3.1	3.0
	Other economically inactive	6.7	6.4	6.4
	Missing	0.0		
Cigarette smoking	Never smoker	44.3	45.7	45.7
	Ex-smoker	24.8	26.2	26.2
	Current, <10/day	10.8	10.9	11.0
	Current, 10-19/day	13.0	13.2	13.2
	Current, 20+/day	3.9	4.0	4.0
	Missing	3.2		
Drinking frequency in last 12 months	4+days/week	19.3	20.3	20.3
	2-3 days/week	31.8	34.2	34.1

	2-3/month-1/week	28.6	29.2	29.2
	less often	12.2	12.0	12.0
	not in last 12 months/non-drinker	4.9	4.3	4.3
	Missing	3.2		
BMI categories	18.5-24.99	33.2	34.7	34.7
	25-29.99	40.5	41.8	41.8
	30-34.99	16.7	16.7	16.6
	35+	7.3	6.4	6.4
	<18.5	0.5	0.5	0.5
	Missing	1.8		
Long-term illness at age 42	No	68.5	72.6	72.5
	Yes	28.3	27.4	27.5
	Missing	3.2		
CIS-R score at 44	Mean (SD)	3.40(4.64)	3.21(4.40)	3.22(4.40)
	% Missing	0.9		
Country at 42	England	82.9	85.3	85.3
	Wales	5.1	4.7	4.7
	Scotland	8.9	10.0	10.0
	Missing	3.1		
Takes medications which could affect inflammation, HRT or oral contraceptives	No	81.8	82.7	82.8
	Yes	18.2	17.3	17.3
*Based on 7692 observations ** Based on 7683 observations				

4.3.2 Results

As shown in Table 4.1, a comparison of participants retained vs. participants excluded found that retained participants were more likely to be male, in RGSC class I or II, less likely to be renting, and more likely to be employed (all $p<0.05$). They were less likely to have a long-term illness and were disproportionately English, drank slightly more, had fewer depressive symptoms and lower BMI, and were less likely to take anti-inflammatory medications, HRT or contraceptives (all $p<0.05$). In the final samples CRP was much lower, largely due to the exclusion of 207 participants with CRP>10mg/L. However, the 439 participants with nonmissing CRP measurements under this cut-off but excluded for other reasons nevertheless had, at 1.91mg/L, higher CRP than other participants in

the normal range (p=0.01), and higher fibrinogen (3.02g/L, p for difference <0.001). Overall, the sample was therefore selected for favourable economic circumstances and good health.

4.3.2.1 Unemployment and Inflammation

Table 4.2 shows that in sex- and country-adjusted models, the three markers of systemic inflammation were raised for unemployed compared to employed participants, but significantly only for fibrinogen (coeff: 0.15, p=0.20, coeff: 0.05, p=0.01, OR: 1.39, p=0.19 for log-transformed CRP, log-transformed fibrinogen and CRP>3mg/L). While additional adjustment for SEP and long-term illness reduced effect sizes, adding health behaviours caused associations with CRP outcomes to strengthen considerably, increasing compared to crude models. Adding CIS-R made almost no difference.

Addition of health behaviours individually to otherwise fully-adjusted models found that BMI was responsible for increase in CRP effects. This was consistent with an analysis of BMI by employment status, which found unemployed participants in the final CRP sample were substantially less likely to be overweight or obese (50.5%) than employed participants (65.9%).

No significant interactions with sex were found.

4.3.2.2 Sensitivity analyses

Associations with unemployment in sex- and country- adjusted models were not significantly different in participants lacking data for further covariates compared to those in the complete-case sample (p=0.71, p=0.75, p=0.98 for log-transformed CRP, log-transformed fibrinogen and CRP>3mg/L) indicating their exclusion had not produced substantial bias.

Exclusion from fully-adjusted models of participants taking potentially anti-inflammatory medications, HRT or contraceptives barely changed effect sizes (coeff: 0.19, p=0.07, coeff: 0.05, p=0.03, OR: 1.57, p=0.14 for log-transformed CRP, log-transformed fibrinogen and CRP>3mg/L respectively), although the drop in precision with exclusion of over 17% of the sample makes a direct

comparison impossible. Adding time of day, season and processing time of blood samples to fully-adjusted models also did not substantially change results coeff: 0.19, p=0.06, coeff: 0.04, p=0.02, OR: 1.46, p=0.17 for log-transformed CRP, log-transformed fibrinogen and CRP>3mg/L).

Table 4.2: Associations of current unemployment with inflammatory markers: whole-sample analysis (NCDS)										
		CRP (mg/L, log-transformed) N=7027			Fibrinogen (g/L, log-transformed) N=7019			CRP>3mg/L N=7027		
Adjustment level		Coeff.	CI	P	Coeff.	CI	p	OR	CI	p
Gender, country	In paid employment	Ref.								
	Unemployed	0.15	-0.08-0.37	0.20	0.05	0.01-0.09	0.01	1.39	0.83-2.31	0.21
	Sick/disabled	0.45	0.30-0.60	<0.001	0.09	0.06-0.11	<0.001	2.43	1.80-3.27	<0.001
	Other economically inactive	-0.06	-0.17-0.05	0.26	0.00	-0.02-0.02	1.00	1.03	0.80-1.33	0.83
	In paid employment	Ref.								
Gender, country and socioeconomic position	Unemployed	0.06	-0.16-0.28	0.59	0.03	-0.01-0.07	0.09	1.15	0.69-1.94	0.59
	Sick/disabled	0.32	0.17-0.47	<0.001	0.06	0.03-0.09	<0.001	1.92	1.41-2.62	<0.001
	Other economically inactive	-0.11	-0.22-0.00	0.04	-0.01	-0.03-0.01	0.23	0.93	0.72-1.20	0.56
	In paid employment	Ref.								
Gender, country, socioeconomic position and long-term illness	Unemployed	0.07	-0.16-0.29	0.56	0.03	0.00-0.07	0.08	1.16	0.69-1.95	0.58
	Sick/disabled	0.23	0.08-0.39	0.00	0.05	0.02-0.07	0.00	1.58	1.15-2.16	0.01
	Other economically inactive	-0.12	-0.23--0.01	0.03	-0.01	-0.03-0.01	0.18	0.90	0.70-1.17	0.45
Gender, country, socioeconomic position, long-term illness and health behaviours	In paid employment	Ref.								
	Unemployed	0.20	0.00-0.40	0.05	0.05	0.01-0.08	0.01	1.46	0.85-2.52	0.17
	Sick/disabled	0.17	0.03-0.31	0.02	0.03	0.00-0.06	0.03	1.47	1.04-2.08	0.03
	Other economically inactive	-0.08	-0.18-0.02	0.12	-0.01	-0.03-0.01	0.28	0.89	0.67-1.18	0.42
Gender, country, socioeconomic position, long-term illness, health behaviours and CIS-R	In paid employment	Ref.								
	Unemployed	0.20	0.00-0.40	0.05	0.05	0.01-0.08	0.01	1.47	0.85-2.53	0.17
	Sick/disabled	0.16	0.02-0.31	0.02	0.03	0.00-0.06	0.02	1.52	1.07-2.17	0.02
	Other economically inactive	-0.08	-0.18-0.02	0.11	-0.01	-0.03-0.01	0.29	0.90	0.67-1.19	0.45

4.3.3 Discussion

This study population had a very small exposed group (N=95 in the final sample), which is unsurprising given the very low background unemployment rate at the time of data collection in 2003[10]. Despite this statistical limitation, in fully-adjusted models log-transformed CRP and fibrinogen were significantly elevated amongst unemployed participants compared to employed counterparts, with a substantial though non-significant elevation in odds of CRP>3mg/L. This finding is consistent with research linking inflammation to social stressors including bereavement[273] caregiving[229] and disadvantaged socioeconomic position[274, 275], and the hypothesis that inflammatory markers may be raised during unemployment as a result of stress pathways. At the same time, the attenuation observed with adjustment for SEP and long-term illness supports the operation of direct and indirect selection in the relationship of unemployment and aspects of health related to inflammation. The lack of significant interactions with gender is however difficult to meaningfully interpret given the very small exposed group, including only 34 unemployed women.

BMI was found to be acting as a suppressor of effects, underscoring the importance of considering health behaviours in the relationship of systemic inflammation and social factors. This presumably results from the fact that adiposity is strongly and positively linked to systemic inflammation, and unemployed participants in this sample were substantially less likely to be overweight or obese than employed participants. That additional adjustment for CIS-R did not attenuate associations is evidence against a substantial relationship of systemic inflammation and overall mental health independent of health behaviours and confounding factors.

4.3.3.1 Limitations

The main limitation of this analysis was the very small exposed group. In addition, while a high proportion of participants present at the biomedical sweep gave blood samples and were included in final models, the NCDS as of the biomedical sweep cannot be considered a nationally representative cohort due to earlier non-random attrition[276], and resultant bias cannot be ruled out.

4.4 Analyses using HSE and SHeS

4.4.1 Methods

4.4.1.1 Participants

The Health Survey for England (HSE) and the Scottish Health Survey (SHeS) are annual government surveys, whose structure and sampling design are described in section 1 of the Methods Chapter. This analysis was restricted to core-sample participants of working age, defined as 16-64 last birthday.

For this analysis, data was aggregated from nine HSE and SHeS surveys at which CRP and fibrinogen measurements were taken for the core sample: HSE 1998, 1999, 2003, 2006 and 2009 and SHeS 2003, 2008, 2009, and 2010. At HSE 1999 and from 2008 in the SHeS only a sub-sample of core sample adults were targeted for a nurse visit, so only these participants had measurements of CRP and fibrinogen. Observations from SHeS 2011 were not used, because introduction of a different CRP analyser resulted in measured CRP concentrations on average 15mmol/L higher, leading to concerns about consistency[257].

The initial sample comprised all core sample working-age adults from nine surveys targeted for a blood sample (N= 49,385). Of these, 43,129(87.3%) consented to a nurse visit but only 30,103 (61.0%) consented to a blood sample. Problems taking samples, laboratory problems with samples obtained, and non-measurement of fibrinogen for participants taking fibrates resulted in 27,366 CRP measurements and 24,551 fibrinogen measurements.

Participants with CRP>10mg/L were excluded from CRP (N=1,453) and fibrinogen analyses (N=1,237). Of remaining observations, 25 participants were missing employment status, with a further 2,863 and 2,568 participants excluded due to missing covariates. The final complete-case sample sizes were 23,025 for CRP models, and 20,724 for fibrinogen models.

4.4.1.2 Measures

Employment status and all covariates except BMI were assessed by questionnaire at the time of blood sample collection. Alcohol intake was assessed by frequency of drinking occasions in the past year (every couple months or less, 1-2 times per month, 1-2 times per week, 3- 4 times per week, 5+ times per week, or never). Long-term illness (mental or physical) was categorized as none, limiting, and non-limiting. Total GHQ-12 score (dichotomized using the standard cut-off of 3+) was included to account for depressive/anxiety symptoms. Non-steroidal anti-inflammatory drugs, systemic corticosteroids, corticosteroid injections, lipid-lowering drugs, beta-blockers, diclofenac sodium for gout, and aspirin or ibuprofen as an analgesic or antiplatelet were classified as medications that would influence inflammatory marker levels.

4.4.1.3 Analysis

All analyses used STATA's svyset command to account for clustering by primary sampling unit. However, analyses were unweighted because the aggregated nature of the dataset meant appropriate weights were not available. Country and year were included as covariates, with 2003 (when large numbers of observations were collected in both countries) as baseline. Since only 166 usable observations came from HSE 1999, this was merged with HSE 1998.

4.4.2 Results

The original and final analytic samples are shown in Table 4.3. Compared to those excluded, participants retained in final models were older and more likely to be male. They were more likely to be employed, less likely to be unemployed, and disproportionately English, of more advantaged SEP by both RGSC and housing tenure, and less likely to have a limiting long-term illness or above-cutoff depressive/anxiety symptoms (all $p<0.001$). They smoked less and drank more, were less likely to be taking anti-inflammatory medications, and had lower BMI ($p<0.001$). CRP and fibrinogen were substantially lower in the final samples, again largely due to the exclusion of participants with

CRP>10mg/L. However, both CRP (at 2.43mg/L) and fibrinogen (at 2.90g/L) were nevertheless higher among participants with CRP<10mg/L but excluded for other reasons compared to the remaining participants in the normal CRP range (both $p < 0.001$). Inflammatory marker levels differed between the surveys, and are shown by survey in Appendix E.

Table 4.3: Descriptive characteristics of the sample (HSE/SHeS)				
		Initial sample (16-64, targeted for blood sample) N= 49,385	Final analytic sample for CRP N= 23,025	Final analytic sample for fibrinogen N=20,724
		%	%	%
Age group	16-31 (Early career)	26.6	20.1	21.3
	32-47 (Mid-career)	37.7	40.4	42.2
	48-64 (Late career)	35.7	39.5	36.5
Gender	Men	45.0	47.3	47.1
	Women	55.0	52.7	52.9
		Mean (SD)	Mean (SD)	Mean (SD)
Inflammatory markers	C-reactive protein*	3.02(6.2)	1.98(2.03)	-
	Fibrinogen**	2.82(0.70)	-	2.76(0.63)
		%	%	%
Occupational social class (RGSC) from current or past employment	i –professional	4.8	5.7	5.8
	ii-managerial-technical	28.4	32.2	32.2
	iii-nm - skilled non-manual	22.7	23.1	23.3
	iii-m - skilled manual	16.7	17.8	17.7
	iv - semi-skilled manual	16.8	16.5	16.5
	v – unskilled manual	5.1	4.8	4.6
	Missing	5.5		
Housing tenure	Owns outright	20.1	22.1	20.9
	Buying with a mortgage/loan	52.5	56.3	57.5
	Council/housing assoc. rented	16.8	12.6	12.2
	Private rented/other	10.4	9.1	9.3
	Missing	0.3		
Economic status	In paid employment	68.0	75.2	76.5
	Unemployed, seeking work	2.9	2.2	2.2
	Sick or disabled	6.2	4.3	3.6
	Other economically inactive	22.7	18.3	17.7
	Missing	0.3		
Cigarette smoking	Never smoker	45.2	45.0	45.5
	Ex-smoker	25.9	28.9	28.2
	Current, <10/day	7.6	7.1	7.1
	Current, 10-19/day	11.4	10.6	10.7
	Current, 20+/day	8.8	8.4	8.5
	Missing	1.0		
Drinking frequency in last 12 months	Every couple months or less	12.7	11.5	11.3
	Once or twice/month	13.2	12.8	12.9
	Once or twice/week	31.2	32.5	33.0
	3 or 4 days/week	15.8	18.0	18.2
	5 days/week or more	16.4	19.0	18.8
	not in last 12 months/non-drinker	10.0	6.2	5.9
	Missing	0.7		
BMI categories	<18.5	1.5	1.1	1.1
	18.5-24.99	34.4	38.1	39.4
	25-29.99	32.9	39.8	39.9
	30-34.99	13.8	15.4	14.6
	35+	6.2	5.6	5.0
	Missing	11.3		
Limiting long-term illness?	No long-term illness	61.5	61.7	64.3
	Limiting long-term illness	21.2	19.6	18.1

	Non-limiting long-term illness	17.2	18.7	17.6
	Missing	0.1		
GHQ-12 score	0-2	76.2	82.1	82.4
	3+	18.2	17.9	17.6
	Missing	5.6		
Survey	HSE 1998	25.6	30.6	31.4
	HSE 1999	0.6	0.7	0.7
	HSE 2003	23.5	23.9	23.9
	HSE 2006	22.0	21.1	20.7
	HSE 2009	7.1	6.3	6.2
	SHeS 2003	12.6	10.9	10.7
	SHeS 2008	2.8	2.2	2.1
	SHeS 2009	2.9	2.3	2.1
	SHeS 2010	2.9	2.2	2.1
Government Office Region	Scotland	21.2	17.5	17.0
	Northeast	4.5	4.6	4.7
	Northwest	11.3	11.9	11.9
	Yorkshire & Humberside	8.2	9.0	8.9
	West Midlands	8.4	8.7	8.9
	East Midlands	7.4	7.9	7.8
	East Anglia	8.8	9.1	9.1
	London	10.1	8.4	8.4
	Southeast	12.5	14.4	14.7
	Southwest	7.7	8.5	8.5
Takes medications which could affect inflammation	Yes	10.5	12.7	7.1
	No	89.5	87.3	92.9
*Based on 27427 observations **Based on 24607 observations				

Unemployment was higher among Scottish participants than English participants at 2.6%, compared to 2.1% in the final CRP sample (Table 4.4). Within England, it was lowest in the Southwest at 1.4%.

Table 4.4: Distribution of employment status (%) in final HSE/SHeS analytic sample (CRP analyses), by country/region

	ALL ENGLISH SURVEYS	**ALL SCOTTISH SURVEYS**	**ENGLAND: Southwest only**
Paid employment	75.6	73.3	74.7
Unemployed	2.1	2.6	1.4
Sick/disabled	4.0	5.8	3.1
Other economically inactive	18.4	18.4	20.7
Total N	18,997	4,028	1,959

4.4.2.1 Unemployment and Inflammation

Across the whole sample log-transformed CRP, log-transformed fibrinogen and odds of CRP>3mg/L were significantly raised for unemployed, compared to employed participants (Table 4.5). Effects were robust to adjustment for age, gender, socioeconomic position, long-term illness, GHQ-12 score, and health behaviours. For all three markers, attenuation occurred with adjustment for SEP (Table 3), but additional adjustment made little difference.

In fully-adjusted models, significant interactions were found for age band and country, although not gender. Age- and country-stratified analyses were conducted to investigate further. Within England, interactions of unemployment and government office region were tested for with the Southeast (the largest group) as baseline.

Table 4.5: Associations of current unemployment with inflammatory markers: whole-sample analysis (HSE/SHeS)										
		CRP (mg/L, log-transformed) N=23,025			Fibrinogen (g/L, log-transformed) N=20,724			CRP>3mg/L N=23,025		
Adjustment level		Coeff.	CI	P	Coeff.	CI	p	OR	CI	p
Age, gender, country, year	In paid employment	Ref.			Ref.			1.0		
	Unemployed	0.22	0.13-0.32	<0.001	0.05	0.03-0.07	<0.001	1.66	1.35-2.03	<0.001
	Sick/disabled	0.42	0.35-0.49	<0.001	0.07	0.06-0.09	<0.001	2.33	2.04-2.66	<0.001
	Other economically inactive	0.05	0.01-0.08	0.01	0.02	0.01-0.03	<0.001	1.21	1.12-1.31	<0.001
Age, gender, country, year, and socioeconomic position	In paid employment	Ref.								
	Unemployed	0.15	0.05-0.24	0.002	0.03	0.01-0.05	0.003	1.44	1.17-1.77	0.001
	Sick/disabled	0.31	0.24-0.38	<0.001	0.05	0.03-0.06	<0.001	1.91	1.66-2.19	<0.001
	Other economically inactive	0.03	-0.00-0.07	0.09	0.01	0.00-0.02	0.02	1.17	1.08-1.27	<0.001
Age, gender, country, year, socioeconomic position, and long-term illness	In paid employment	Ref.								
	Unemployed	0.14	0.04-0.23	0.004	0.03	0.01-0.05	0.004	1.41	1.15-1.74	0.001
	Sick/disabled	0.19	0.12-0.27	<0.001	0.03	0.02-0.05	<0.001	1.55	1.33-1.81	<0.001
	Other economically inactive	0.02	-0.02-0.06	0.27	0.01	0.00-0.02	0.03	1.14	1.06-1.24	0.001
Age, gender, country, year, socioeconomic position, long-term illness, and health behaviours	In paid employment	Ref.								
	Unemployed	0.13	0.05-0.22	0.002	0.02	0.00-0.04	0.03	1.42	1.13-1.77	0.002
	Sick/disabled	0.17	0.10-0.24	<0.001	0.02	0.01-0.04	0.005	1.56	1.32-1.84	<0.001
	Other economically inactive	0.04	0.01-0.08	0.02	0.01	0.00-0.02	0.004	1.19	1.09-1.30	<0.001
Age, gender, country, year, socioeconomic position, long-term illness, health behaviours, and GHQ-12	In paid employment	Ref.								
	Unemployed	0.13	0.05-0.22	0.002	0.02	0.00-0.04	0.03	1.40	1.13-1.75	0.003
	Sick/disabled	0.17	0.10-0.24	<0.001	0.02	0.01-0.04	0.008	1.53	1.30-1.81	<0.001
	Other economically inactive	0.04	0.01-0.08	0.02	0.01	0.00-0.02	0.005	1.19	1.09-1.29	<0.001

4.4.2.2 Stratification by age band, country and region

Associations of unemployment with CRP and fibrinogen were significantly stronger for participants aged 48-64, compared to those aged 16-31 (interaction p=0.003 and p=0.001 respectively). Stratification by age band (Table 4.6) showed that associations with all three markers were strong for those aged 48 and over, but non- significant in the younger groups.

Table 4.6: Fully adjusted* associations of current unemployment with inflammatory markers in whole HSE/SHES sample, stratified by age group

AGE BAND		Coeff./OR	CI	P	N (unemployed)	N (total)
16-31	Log CRP	0.08	-0.07-0.25	0.29	188	4621
	Log fibrinogen	0.01	-0.02-0.04	0.53	177	4411
	CRP, dichotomized	1.21	0.81-1.85	0.34	188	4621
32-47	Log CRP	0.06	-0.08-0.20	0.39	171	9309
	Log fibrinogen	0.00	-0.03-0.03	0.92	165	8747
	CRP, dichotomized	1.32	0.89-1.98	0.17	171	9309
48-64	Log CRP	0.27	0.12-0.41	<0.001	146	9095
	Log fibrinogen	0.07	0.03-0.10	<0.001	120	7566
	CRP, dichotomized	1.56	1.07-2.26	0.02	146	9095

*Adjusted for age in years, gender, country, survey year, occupational social class, housing tenure, presence of a long-term illness, smoking, alcohol consumption, categorized BMI and dichotomized GHQ-12

Associations with CRP and fibrinogen were considerably stronger for Scottish participants (interactions p<0.001 and p=0.009). Stratification by country (Table 4.7) showed that among English participants, only odds of CRP>3mg/L was close to significantly raised for unemployed participants after full adjustment, but in Scotland associations with all three measures of inflammation were robust. Within England, there were significant regional interactions for CRP and fibrinogen (interactions p=0.04 and p=0.02). This was driven by differences in the Southwest, where associations of all three inflammatory markers with unemployment were found to be negative (Table 4.7).

Table 4.7:Fully adjusted* associations of current unemployment with inflammatory markers, all age groups, stratified by country/region (HSE/SHeS)

		Coeff./OR	CI	P	N (unempl)	N (Total)
SCOTLAND	Log CRP	0.41	0.22-0.60	<0.001	102	4038
	Log fibrinogen	0.07	0.03-0.11	<0.001	95	3522
	CRP, dichotomized	1.88	1.17-3.06	0.009	102	4038
		Coeff./OR	CI	P	N (unempl)	N (Total)
ENGLAND	Log CRP	0.06	-0.04-0.16	0.23	399	18997
	Log fibrinogen	0.01	-0.01-0.03	0.48	365	17202
	CRP, dichotomized	1.28	0.99-1.64	0.06	399	18997
ENGLAND – Southwest only	Log CRP	-0.35	-0.63 - -0.07	0.02	28	1959
	Log fibrinogen	-0.08	-0.13 - -0.02	0.007	27	1763
	CRP, dichotomized	0.51	0.16-1.68	0.27	28	1959

*Adjusted for age in years, gender, country, survey year, occupational social class, housing tenure, presence of a long-term illness, smoking, alcohol consumption, categorized BMI, and dichotomized GHQ-12

Table 4.8: Elevations in inflammatory markers, unemployed vs. employed participants: England and Scotland separately									
ENGLAND ONLY	CRP (mg/L, log-transformed) N=18997			Fibrinogen (g/L, log-transformed) N=17202			CRP>3mg/L N=18997		
Adjustment level	Coeff.	CI	P	Coeff.	CI	p	OR	CI	p
Age, gender, year	0.12	0.02-0.23	0.02	0.03	0.01-0.06	0.004	1.47	1.16-1.86	0.001
+ socioeconomic position	0.06	-0.05-0.17	0.27	0.01	-0.01-0.04	0.23	1.31	1.03-1.66	0.03
+ socioeconomic position and long-term illness	0.05	-0.06-0.16	0.35	0.01	-0.01-0.04	0.27	1.28	1.01-1.63	0.04
+ socioeconomic position, long-term illness, and health behaviours	0.06	-0.04-0.15	0.24	0.01	-0.01-0.03	0.46	1.28	1.00-1.65	0.05
+ socioeconomic position, long-term illness, health behaviours, and GHQ-12	0.06	-0.04-0.16	0.23	0.01	-0.01-0.03	0.48	1.28	0.99-1.64	0.06
SCOTLAND ONLY	CRP (mg/L, log-transformed) N=4028			Fibrinogen (g/L, log-transformed) N=3522			CRP>3mg/L N==4028		
Adjustment level	Coeff.	CI	P	Coeff.	CI	p	OR	CI	p
Age, gender, year	0.58	0.40-0.76	<0.001	0.12	0.08-0.16	<0.001	2.49	1.65-3.75	<0.001
+ socioeconomic position	0.49	0.30-0.67	<0.001	0.10	0.06-0.14	<0.001	2.07	1.36-3.13	0.001
+ socioeconomic position and long-term illness	0.48	0.30-0.67	<0.001	0.10	0.06-0.14	<0.001	2.06	1.35-3.14	0.001
+ socioeconomic position, long-term illness, and health behaviours	0.41	0.23-0.60	<0.001	0.07	0.03-0.11	<0.001	1.90	1.19-3.04	0.007
+ socioeconomic position, long-term illness, health behaviours, and GHQ-12	0.41	0.22-0.60	<0.001	0.07	0.03-0.11	<0.001	1.88	1.17-3.06	0.009

4.4.2.3 Sensitivity analyses

Age-, gender-, country-, and year-adjusted associations between unemployment and inflammatory markers did not differ between participants lacking covariate data and other participants, indicating their exclusion had not produced bias. Associations did not differ between participants taking anti-inflammatory medicines other participants, indicating their inclusion had not produced bias. Since years of data collection differed between the two countries, we considered whether country differences might reflect secular changes in associations of unemployment and health due to the recession. Analyses were re-run restricted to 2003, a year well before the recession when large

numbers of observations were taken in both countries, but country interactions remained for both CRP (p=0.01) and fibrinogen (p=0.06).

To explore whether country/ regional differences were due to climate, English observations were stratified into latitudinal bands: The North West, North East and Yorkshire, the Midlands and East Anglia, and London and the South. No latitude effect was observed.

In both countries (Table 4.8, Table 4.9), attenuation occurred with adjustment for SEP on all measures of inflammation. In contrast, additional adjustment for long-term illness made no difference in either country. Adjustment for health behaviours produced modest attenuation in Scotland, but not England.

It was not possible to explore the impact was explored of adding time of day, season and processing time of blood sample collection to models, since this information was not available for all surveys.

4.4.3 Discussion

4.4.3.1 Unemployment and inflammation

In a large dataset representing working-age people in England and Scotland, we found elevations in CRP and fibrinogen among unemployed men and women, compared to employed counterparts. Results were robust to adjustment for pre-existing illness, social position, health behaviours and symptoms of depression/anxiety. This suggests unemployment is linked to inflammation via pathways independent of these factors, and that inflammation may help explain the increased morbidity and mortality repeatedly observed in this group.

These findings, like the results in the NCDS, accord with research linking inflammation to social stressors including bereavement[273] caregiving[229] and disadvantaged socioeconomic position[274, 275]. These results do not support a model whereby the poor health of the unemployed can be explained by direct selection due to poor health. However, in both countries

substantial attenuation occurred with adjustment for SEP, supporting indirect selection by socioeconomic position.

While unemployment is associated with adverse health behaviours[277], in our study this did not explain the association of unemployment with raised inflammatory markers. Modest attenuation with adjustment for smoking, drinking, and BMI was observed in Scotland, but not England. This may reflect inaccuracies in measurement of tobacco and alcohol consumption in large-scale health surveys, limiting how effectively these factors can be controlled for. Alternatively, results may support the idea that the relationship of unemployment with health behaviours may itself vary by context[146].

4.4.3.2 Age and country/regional effects

The age modification observed could reflect unemployment being more stressful for older jobseekers, for instance due to outdated skills, or real or perceived job discrimination[2]. Alternatively, it could reflect accumulation of exposure over the life-course. There is substantial evidence that unemployment spells cluster longitudinally within individuals, due to loss of skills or impact on perceived employability[16, 17]. There is also evidence that effects of unemployment on inflammation are lasting and could act additively over time[119]. Hence, late-career unemployment may be acting as a marker for longer-term unemployment and/or more past unemployment, with plausibly greater effects on inflammation.

It is unclear what is driving the country/regional modifications. Sensitivity analyses allowed us to discount differential medication use by country, proximity of data collection to the recession and latitude as explanations. Furthermore, country differences are not consistent with differential selection effects due to variation in background unemployment rate. 'Direct selection' – the idea

that poor health of the unemployed can be largely explained by selection into unemployment of the unhealthy, and/or selection of the healthier unemployed back into employment – predicts weaker associations of unemployment and ill-health in times and places when unemployment is higher. Against a high background unemployment rate, job loss should be less discriminating, selection minimized, and the unemployed more 'normal' as a result[105]. Since unemployment benefit rates are determined by central UK government, country effects are unlikely to stem from differential financial impacts of unemployment. Hence, if the differences are not due to any of these processes and persist after full adjustment, results may implicate a genuinely greater impact of unemployment in Scotland via alternative pathways such as psychosocial stress.

While selection predicts stronger associations of unemployment and ill-health against a low background unemployment rate, there are also theoretical reasons to expect the opposite. It has been suggested that unemployment may be a more stressful experience with worse effects on health where unemployment is high, because jobseekers will perceive prospects for re-employment as worse[212]. This could produce stronger associations of unemployment and ill-health, despite weaker selection effects.

A final possibility is that country and regional differences may again reflect life-course accumulation processes. If unemployment was more widespread in Scotland at the time of data collection and had been during much of these participants' working lives, then it is likely that unemployed Scottish participants will have been unemployed for longer than their counterparts elsewhere, or accumulated more lifetime unemployment, with plausibly greater effects on inflammation. Indeed, this explanation is supported by the stronger associations observed for older participants, since differences stemming from accumulation processes would be expected to emerge later in life.

While this cannot be tested within this cross-sectional dataset, support comes from other UK data sources from this period. An analysis of unemployment duration between 1991 and 2006 using the

British Household Panel Survey[211] found probability of re-employment during follow-up was lower in Scotland than every English region (0.655, compared to the Southeast).

The negative effects in the Southwest require a different explanation. Unemployed participants in the Southwest did not appear different in terms of demographics or health behaviours, but this region had the least unemployment, in accordance with Labour Force Survey data from this period. It is therefore likely that these participants will have been unemployed for less time than their counterparts elsewhere, perhaps with better perceptions of re-employment prospects playing an additional protective role. However, these factors cannot explain why inflammatory markers were actually lower for unemployed compared to employed participants in this region.

Given the small sample sizes in regionally-stratified models, negative effects in the Southwest could be type 1 errors. Alternatively, differences in three-way selection between the employed, unemployed, and economically inactive could be involved. For people with sufficient health problems to claim sickness/disability benefits, the financial incentive to exit the labour market altogether is considerably greater for those who are unemployed than employed, and people do appear to follow these incentives[278]. Such differential labour market exit would mean that, all else equal, the unemployed should be more selected for *good* health than the employed. Of course, other processes – such as selection of healthy jobseekers back into employment, plus any negative causal influences of unemployment on health – would act in the opposite direction, potentially obscuring effects of differential labour market exit. But in a context of very low unemployment, these effects could plausibly come to the fore, possibly accounting for the negative associations in the Southwest. If so, effects reported for Scotland, and England overall, should be considered underestimates.

4.4.3.3 Limitations

This analysis had several advantages; the sample was much larger than previous studies, and contained both men and women from across the working-age range, increasing generalizability of

results. By considering a wide range of potential confounders and mediators, it was possible to explore confounding by socioeconomic position, by pre-existing illness, and the role of health behaviours. Participants who were temporarily sick during a spell of unemployment were excluded, leading to conservative estimates.

This analysis has three main limitations. The first concerns loss of data between those targeted for a blood sample and the usable CRP and fibrinogen measurements obtained; resultant bias cannot be ruled out. Secondly, comparatively few unemployed women in the sample meant gender modifications could not be fully explored. Thirdly, analysis of current unemployment in the context of life histories was not possible. This would have allowed further exploration of effect modifications by age and region.

4.5 Analyses using Understanding Society

4.5.1 Methods

4.5.1.1 Participants

The cross-sectional analysis began using all participants of working age (16-64) who were present at the nurse visit, which occurred during W2 for the new UKHLS component of the sample and during W3 for the BHPS component of the sample. This allowed a considerably greater sample size than the longitudinal analyses, which were restricted to members of the smaller BHPS component who had been present since 1991. However, of the 15473 working-age participants present at the nurse visit, only 9,509 (61%) gave blood. Cross-sectional blood weights were applied to take account of non-random non-response to blood sample, which meant effective exclusion of a further 8.2% of participants who had been assigned zero-value weights. 465 participants were excluded because their CRP exceeded 10mg/L. Exclusions for missing covariates resulted in a final sample size of 6461 for CRP analyses and 6357 for fibrinogen analyses.

4.5.1.2 Measures

Because the nurse visit occurred approximately 5 years after the mainstage interviews, employment status was obtained by considering reports of current and former activities within the past year from the wave following that including the nurse visit (W3 for new UKHLS participants, W4 for BHPS participants). For the small group who had dropped out by the next wave, current employment status as reported at W2/W3 was used. Since smoking and drinking were not asked about at W3, information on those covariates came from W2 for all participants and are effectively proxy measures for the BHPS component of the sample. NSAIDs, statins, betablockers, lipid-lowering drugs for cholesterol or fibrinogen, anti-fibrolytics or haemostatics, prescribed aspirin, oral contraceptives, or hormone replacement therapy were classified as medications which could affect inflammation or fibrinogen specifically.

Alcohol consumption was classified as most days, 3-4 days/week, 2-3 days/week, 1/month- 1/week, <1/month, or non-drinker. Long-term illness (physical or mental) was included as a binary variable, since information on whether this was limiting was not available.

4.5.1.3 Analysis

Using STATA's svyset command, all analyses took account of clustering by primary sampling unit and strata. Cross-sectional weights were used to take account of non-random non-response to the nurse visit.

Table 4.9: Descriptive characteristics of the sample (UKHLS)				
		Initial sample: present and aged 16-64 at nurse wave N=15473	Final sample (CRP)[+] N=6461	Final sample (Fibrinogen)[+] N=6357
		(%)	(%)	(%)
Age at nurse visit	15-31	22.6	15.0	15.0
	32-47	36.6	37.4	37.4
	48-64	40.9	47.5	47.6
Sex	Male	43.0	44.6	55.5
	Female	57.0	55.4	44.5
		Mean (SD)	Mean (SD)	Mean (SD)
Inflammatory markers	C-reactive protein*	2.87(5.89)	1.90(1.97)	-
	Fibrinogen**	2.72(0 .59)	-	2.67(0.54)
		%	%	%
Country	England	85.2	88.3	88.2
	Wales	6.7	2.8	2.8
	Scotland	8.0	9.0	9.0
Employment status	Employed	68.3	75.9	75.9
	Unemployed	5.5	4.0	4.0
	Sick/disabled	4.9	3.2	3.3
	Other Econ. Inactive	21.3	17.0	16.9
	Missing	0.1		
SEP: housing tenure	Owns outright	20.6	23.8	23.8
	Buying w/ mortgage	48.0	54.1	54.1
	Council rented	14.7	11.5	11.5
	Private rented/other	12.5	10.7	10.6
	Missing	4.3		
SEP: occupational social class	Professional	4.7	5.7	5.7
	Managerial	30.3	36.5	36.4
	Skilled non-manual	20.7	21.7	21.8
	Skilled manual	16.4	18.2	18.2
	Semi-skilled	14.1	14.3	14.3
	Unskilled	3.8	3.6	3.6
	Missing	10.0		
Long-term illness	No	65.0	68.7	68.7
	Yes	30.8	31.3	31.3
	Missing	4.2		
GHQ	0-2	72.9	81.2	81.2
	3+	18.9	18.8	18.9
	Missing	8.2		
Smoking	Never smoker	41.9	41.6	41.6
	Ex-smoker	33.4	37.4	37.4
	Current, ≤10/day	11.2	10.6	10.6
	Current, 11-20/day	9.3	8.9	8.9
	Current, >20/day	1.8	1.6	1.6
	Missing	2.3		
BMI	18.5-24.9	33.3	32.0	31.7
	25.0-29.9	35.3	38.4	38.6
	30.0-34.9	18.0	19.0	19.0
	>35.0	11.2	9.7	9.8
	<18.5	1.5	0.9	0.9
	Missing	0.7		
Drinking frequency	Most days	11.3	14.8	14.9
	3-4 days/week	13.6	18.6	18.5

	2-3 days/week	26.2	31.4	31.4
	1/month- 1/week	14.7	16.0	16.0
	<1/month	15.6	16.8	16.9
	Non-drinker	2.4	2.4	2.4
	Missing	16.1		
Anti-inflammatory meds/fibrates	No	89.6	89.4	89.3
	Yes	10.4	10.6	10.7
Use of contraceptives/HRT	No	98.2	98.1	98.1
	Yes	1.8	1.9	1.9
[+]Present at nurse wave, excluding CRP>10mg/L and assigned non-zero weights *Based on 9,509 observations **Based on 9471 observations				

4.5.2 Results

A description of the initial and final samples is shown in Table 4.10. Compared to those excluded, retained participants were significantly older, more likely to be male, disproportionately English, and of more advantaged SEP by both RGSC and housing tenure (all p<0.001). While they were less likely to have above-cutoff GHQ (p<0.001), they were not more likely to have a long-term illness or take anti-inflammatory medications, HRT or oral contraceptives, nor did they differ overall with respect to smoking or BMI. They drank more (p<0.001) and were more likely to be employed and less likely to be unemployed (p<0.001). As with the other surveys CRP and fibrinogen were substantially lower in the final samples due to exclusion of participants with CRP>10mg/L. However, mean values were not elevated among participants excluded for other reasons compared to other participants in the normal CRP range.

4.5.2.1 Unemployment and inflammation

Moderate associations between current unemployment and inflammatory markers were observed in models adjusted for age sex and country, although for the two continuous outcomes they were not significant. Associations with all three markers were however entirely explained by socioeconomic position (Table 4.11).

No interactions were found between unemployment and gender. An interaction with age group was found for odds of CRP>3mg/L, with unemployed participants in the mid-career age group of 32-47 (N=2,380, of whom 83 were unemployed) at significantly (p=0.02) higher odds of CRP>3mg/L than counterparts aged 16-31. Stratified models were run to investigate further. While in crude models the effect size for unemployed participants aged 32-47 was OR=2.26, p=0.002 compared to employed counterparts, this was largely explained with adjustment for socioeconomic position (attenuation to OR=1.53, p=0.12). No such effects were seen even in crude models for this age group for log-transformed CRP or fibrinogen.

4.5.2.2 Results of sensitivity analyses

Adding the season, time of day and processing time of blood samples to fully-adjusted models did not alter conclusions at all. Defining the employed baseline group more narrowly to include only fulltime employees did not alter conclusions at all; the coefficient for log-transformed CRP increased while the coefficient for fibrinogen decreased, but neither was significant (p=0.37 and p=0.83 respectively). Exclusion of participants taking medications expected to affect CRP or fibrinogen appeared to increase effect sizes for the continuous outcomes, to coeff 0.08, p=0.28 for CRP and coeff 0.03, p=0.07 for fibrinogen in fully-adjusted models, although the resultant drop in precision with exclusion of 12.2% of the sample makes direct comparison impossible.

Because this analysis was weighted, in contrast to both the NCDS and HSE/SHeS analyses, it was possible that weighting explained the lack of robust associations in this study. Fully-adjusted models were therefore re-run without using sampling weights, but this did not change conclusions.

Analyses were also repeated using an alternative categorization of employment status, in which the baseline group was defined more narrowly as only full-time employees. This showed that changing composition of the baseline group also did not explain the discrepancy between these results and those of the NCDS and HSE/SHeS analyses; inflammatory markers appeared slightly (although not

significantly lower for the new part-time and self-employment workers compared to full-time employed counterparts.

4.5.3 Discussion

In contrast to the NCDS and HSE/SHeS analyses, initial elevations in inflammatory markers for unemployed participants in this population were entirely explained by SEP. This does not support an effect of unemployment on systemic inflammation which is independent of confounding factors. Fully-adjusted associations did not significantly differ by gender or age group, indicating that the lack of associations was not restricted to certain demographic parts of the sample. It is unclear what is causing the discrepancy of effects between UKHLS participants and the other studies.

4.5.3.1 Limitations

The main limitation of this analysis concerns the substantial loss of participants between those eligible for a blood sample and those for whom usable CRP and fibrinogen measurements were received (58.2%). While the use of weights should have reduced resultant bias, the final sample was the smallest of the three analyses and a considerable loss of power was unavoidable.

Table 4.10: Associations of current unemployment with inflammatory markers: whole-sample analysis (UKHLS)										
		CRP (mg/L, log-transformed) N=6461			Fibrinogen (g/L, log-transformed) N=6357			CRP>3mg/L N=6461		
Adjustment level		Coeff.	CI	P	Coeff.	CI	p	OR	CI	p
Age, gender, country	In paid employment	Ref.								
	Unemployed	0.11	-0.09-0.30	0.20	0.03	0.00-0.07	0.05	1.22	0.82-1.82	0.28
	Sick/disabled	0.38	0.19-0.57	<0.001	0.09	0.06-0.13	<0.001	2.22	1.51-3.26	<0.001
	Other economically inactive	0.04	-0.05-0.12	0.36	0.02	0.01-0.04	<0.001	1.19	0.97-1.45	0.06
Age, gender, country, socioeconomic position	In paid employment	Ref.								
	Unemployed	-0.01	-0.17-0.16	0.93	0.02	-0.02-0.05	0.38	0.96	0.67-1.38	0.84
	Sick/disabled	0.23	0.05-0.40	0.01	0.06	0.03-0.10	<0.001	1.53	1.05-2.22	0.03
	Other economically inactive	0.02	-0.06-0.10	0.68	0.02	0.00-0.03	0.02	1.12	0.93-1.34	0.23
Age, gender, country, SEP, and long-term illness	In paid employment	Ref.								
	Unemployed	-0.02	-0.19-0.14	0.79	0.01	-0.02-0.05	0.40	0.93	0.65-1.33	0.68
	Sick/disabled	0.13	-0.05-0.31	0.15	0.06	0.02-0.09	<0.001	1.25	0.86-1.84	0.25
	Other economically inactive	0.01	-0.07-0.09	0.79	0.02	0.00-0.03	0.02	1.10	0.92-1.32	0.31
Age, gender, country, SEP, long-term illness, and health behaviours	In paid employment	Ref.								
	Unemployed	0.01	-0.13-0.16	0.85	0.01	-0.02-0.04	0.51	0.93	0.64-1.34	0.69
	Sick/disabled	0.13	-0.02-0.29	0.08	0.04	0.01-0.08	0.02	1.20	0.80-1.80	0.37
	Other economically inactive	0.03	-0.04-0.29	0.41	0.02	0.00-0.03	0.01	1.12	0.91-1.37	0.29
Age, gender, country, SEP, long-term illness, health behaviours, and GHQ	In paid employment	Ref.								
	Unemployed	0.02	-0.13-0.16	0.83	0.01	-0.02-0.04	0.53	0.93	0.64-1.35	0.71
	Sick/disabled	0.14	-0.02-0.29	0.08	0.04	0.00-0.08	0.03	1.22	0.81-1.82	0.34
	Other economically inactive	0.03	-0.04-11	0.41	0.02	0.00-0.03	0.01	1.12	0.91-1.37	0.28

4.6 Meta-analysis

An individual participant data, two-stage meta-analysis was then conducted across all datasets using ipdmetan in STATA. The Health Survey for England and Scottish Health Surveys were examined as separate studies; in order to examine country effects the Scottish and Welsh components of NCDS and UKHLS were treated separately from the English components. In the analysis combining HSE and SHeS data only, SHeS 2011 had not been included because use of a different CRP analyser had led to concerns about consistency. SHeS 2011 data was however included in the meta-analysis, since this was set up to allow random effects. This resulted in a total of 15 study populations.

Again, participants who were not of working age (16-64) or with CRP>10mg/L were excluded from analysis. Further exclusions for missing CRP and fibrinogen, employment status and covariates resulted in combined complete-case sample size of 38,213 for CRP analyses and 35,796 for fibrinogen analyses. However, the requirement of ipdmetan (like other meta-analytic commands in STATA) to have a binary exposure meant that economically inactive participants needed to be excluded for unemployed participants to be compared to employed participants. This resulted in a final sample size of 30661 for CRP analyses and 29074 for fibrinogen analyses (Table 4.12).

The meta-analysis was adjusted for all covariates used in the three constituent analyses with three exceptions. Since the studies had been delineated by country, it was not necessary to adjust for country given that in the first stage of the meta-analysis study-specific comparisons are calculated. Similarly, since with the exception of UKHLS (2010-2012) studies all took place in a single year, it would not be appropriate to adjust for year. However, effect modification by country or historical period (pre- or post- recession, using 2009 as a cut-off) was examined using stratified meta-analysis. Lastly, mental health at the time of blood sample collection had been indexed by GHQ in the HSE, SHeS and UKHLS but the CIS-R at the NCDS biomedical sweep, it was not possible to adjust for this consistently across the study populations (it should be noted however that adjustment for mental health made almost no difference to effect sizes in individual analyses, minimising resultant bias).

Meta-analytic models were therefore adjusted for sex, age in years, RGSC, housing tenure, long-term illness, smoking, alcohol consumption, and BMI. All covariates were categorised in the same way as in constituent analyses with the exception of alcohol consumption; the use of different categories for drinking frequency meant it was not possible to categorise this other than simply as drinker/non-drinker across the studies. Similarly, in sensitivity analyses it was only possible to explore the impact of excluding participants regularly taking NSAIDs, beta-blockers, corticosteroids, fibrates/anti-fibrolytics/anti-haemostatics, ibuprofen, and aspirin because hormone replacement therapy and contraceptives had not been asked about at all HSE waves.

Table 4.11: Contribution of studies to meta-analysis (complete-case samples)

	CRP Analyses		Fibrinogen Analyses	
STUDY	N (total)	N (unemployed)	N (total)	N (unemployed)
HSE 1998/9	5727	165	5377	155
HSE 2003	4406	94	4046	83
HSE 2006	3814	103	3434	88
HSE 2009	1163	51	1050	48
SHeS 2003	1915	67	1741	61
SHeS 2008	398	9	340	9
SHeS 2009	421	19	369	15
SHeS 2010	405	15	355	16
SHeS 2011	331	22	303	21
NCDS 2003 (England)	5488	75	5480	75
NCDS 2003 (Scotland)	621	17	621	17
NCDS 2003 (Wales)	294	4	294	4
UKHLS 2010-11 (England)	4988	258	4972	259
UKHLS 2010-11 (Scotland)	523	22	521	22
UKHLS 2010-11 (Wales)	167	12	171	12
OVERALL	**30661**	**933 (3.0%)**	**29074**	**888 (3.1%)**

4.6.1 Results

4.6.1.1 Pooled estimates

Pooled estimates showed that all three markers of systemic inflammation were significantly raised for unemployed compared to employed participants after full adjustment (Table 4.13, below). There was moderate heterogeneity of effects across the 15 studies, with I^2 ranging from 32.5% for fibrinogen to 42.6% for odds of CRP>3mg/L. Interactions in the pooled dataset with age group (16-31/32-47/48-64) were tested for, but were not supported (interaction p=0.31, p=0.72, p=0.33 for log-transformed CRP, log-transformed fibrinogen and CRP>3mg/L respectively). Similarly, no interactive effects were observed for gender (interaction p=0.43, p=0.37, p=0.81).

4.6.1.2 Stratification by country and year

Stratification by country (Table 4.14, below) revealed significant effects in all three countries, but these differed substantially in magnitude. For all three outcomes the smallest effects were found in England, intermediate effects in Scotland and the strongest effects in Wales, although the small sample sizes in the Welsh components mean those results should be interpreted with caution. As a result, within-country heterogeneity was substantially less than overall heterogeneity, with the exception of Wales where the lack of precision led to a within-country I^2 of 59.6% for CRP>3mg/L.

Pooled estimates for Southwest England were not significantly negative for any of the inflammatory markers (log-transformed CRP: coeff=-0.11, p=0.40, log-transformed fibrinogen: coeff=-0.01, p=0.74, CRP>3mg/L: OR=0.94, p=0.89).

In contrast to the country effects, stratification by year (Table 4.14) showed that onset of the recession failed to account for much heterogeneity between the studies; effect sizes for all three markers were similar across the two time periods, and within-period heterogeneity was not lower than in the meta-analysis as a whole.

Sensitivity analyses

In age- and sex- adjusted models, effect sizes were not significantly different for participants missing remaining covariates (interaction for log-transformed CRP: p=0.15, log-transformed fibrinogen p=0.47, CRP>3mg/L: p=0.72), indicating their exclusion had not produced bias. Excluding participants regularly taking NSAIDs, beta-blockers, corticosteroids, fibrates, aspirin, or ibuprofen from the whole-sample analysis did not change results (log-transformed CRP: coeff=0.16, p<0.001, log-transformed fibrinogen: coeff=0.04, p<0.001, CRP>3mg/L: OR=1.50, p=0.001).

Table 4.12: Association of current unemployment with biomarkers, by individual study									
	Log-transformed CRP			Log-transformed fibrinogen			CRP>3mg/L		
	Coeff	CI	Weight (%)	Coeff	CI	Weight (%)			Weight (%)
HSE 1998/9	0.10	-0.06-0.26	12.54	0.01	-0.02-0.05	12.48	1.51	1.02-2.23	13.70
HSE 2003	0.02	-0.17-0.21	10.88	0.01	-0.03-0.06	9.59	1.17	0.68-2.03	10.63
HSE 2006	0.43	0.21-0.66	9.29	0.08	0.03-0.13	8.22	2.07	1.13-3.77	9.74
HSE 2009	0.11	-0.08-0.29	11.12	0.02	-0.03-0.06	9.80	1.42	0.88-2.29	11.89
SHeS 2003	-0.03	-0.65-0.60	2.12	0.00	-0.11-0.10	2.74	1.05	0.19-5.98	2.07
SHeS 2008	0.04	-0.22-0.31	7.77	0.02	-0.02-0.07	9.17	0.94	0.42-2.09	7.03
SHeS 2009	0.49	0.04-0.95	3.65	0.06	-0.04-0.15	3.15	1.68	0.52-5.42	4.04
SHeS 2010	0.55	0.09-1.00	3.59	0.14	0.05-0.23	3.48	2.69	0.70-10.34	3.22
SHeS 2011	0.42	-0.02-0.86	3.79	0.07	-0.01-0.15	4.14	5.59	1.80-17.31	4.28
NCDS 2003 (England)	0.17	-0.06-0.39	9.32	0.04	0.00-0.08	10.66	1.27	0.67-2.40	9.16
NCDS 2003 (Scotland)	0.11	-0.37-0.60	3.29	0.04	-0.06-0.13	3.38	1.67	0.46-6.03	3.49
NCDS 2003 (Wales)	1.09	0.12-2.05	0.94	0.20	0.02-0.38	0.93	45.08	3.47-585.1	1.01
UKHLS 2010-11 (England)	0.07	-0.05-0.19	14.74	0.02	-0.01-0.04	16.62	1.08	0.77-1.51	14.84
UKHLS 2010-11 (Scotland)	-0.17	-0.58-0.24	4.29	0.02	-0.07-0.11	3.43	0.34	0.07-1.71	2.33
UKHLS 2010-11 (Wales)	0.45	-0.10-0.99	2.66	0.15	0.03-0.26	2.21	4.09	0.87-19.14	2.55
OVERALL	**0.17**	**0.07-0.26**	**100.00**	**0.04**	**0.02-0.05**	**100.00**	**1.50**	**1.15-1.96**	**100.00**
P for overall effect:	p=0.001			p<0.001			p=0.003		
Overall heterogeneity:	I^2=42.6%			I^2= 32.5%			I^2=42.4%		

Table 4.13: Association of current unemployment with biomarkers across all studies, stratified by country and year
Reference group: employed participants

COUNTRY STRATIFICATION					
	Coeff/OR	CI	Weight (%)	Subgroup effect p	Within-strata heterogeneity (I^2)
Log-transformed CRP					
ENGLAND	0.08	0.01-0.15	66.4%	0.03	0.0%
SCOTLAND	0.29	0.09-0.49	30.0%	0.005	39.8%
WALES	0.64	0.06-1.21	3.6%	0.03	21.2%
Log-transformed Fibrinogen					
ENGLAND	0.02	0.00-0.03	68.3	0.01	0.0%
SCOTLAND	0.06	0.03-0.09	28.5	<0.001	0.0%
WALES	0.16	0.06-0.26	3.1	0.001	0.0%
Odds of CRP>3mg/L:					
ENGLAND	1.24	1.02-1.50	67.2	0.03	0.0%
SCOTLAND	1.89	1.11-3.22	29.2	0.02	30.8%
WALES	10.82	1.07-109.0	3.6	0.04	59.6%
YEAR STRATIFICATION					
Log-transformed CRP	Coeff/OR	CI	Weight (%)	Subgroup effect p	Within-strata heterogeneity (I^2)
1998-2008	0.16	0.04-0.28	59.5	0.01	43.1%
2009-2012	0.20	0.02-0.38	40.5	0.03	49.8%
Log-transformed Fibrinogen					
1998-2008	0.03	0.01-0.05	57.8	0.005	20.4%
2009-2012	0.05	0.02-0.09	42.2	0.005	49.6%
Odds of CRP>3mg/L:					
1998-2008	1.51	1.15-1.98	61.7	0.003	23.5%
2009-2012	1.58	0.89-2.80	38.3	0.12	57.8%

4.6.2 Forest plots: unemployment and inflammatory markers in whole sample, by county and year

Figure 4.1: Unemployment and CRP across all studies, by country

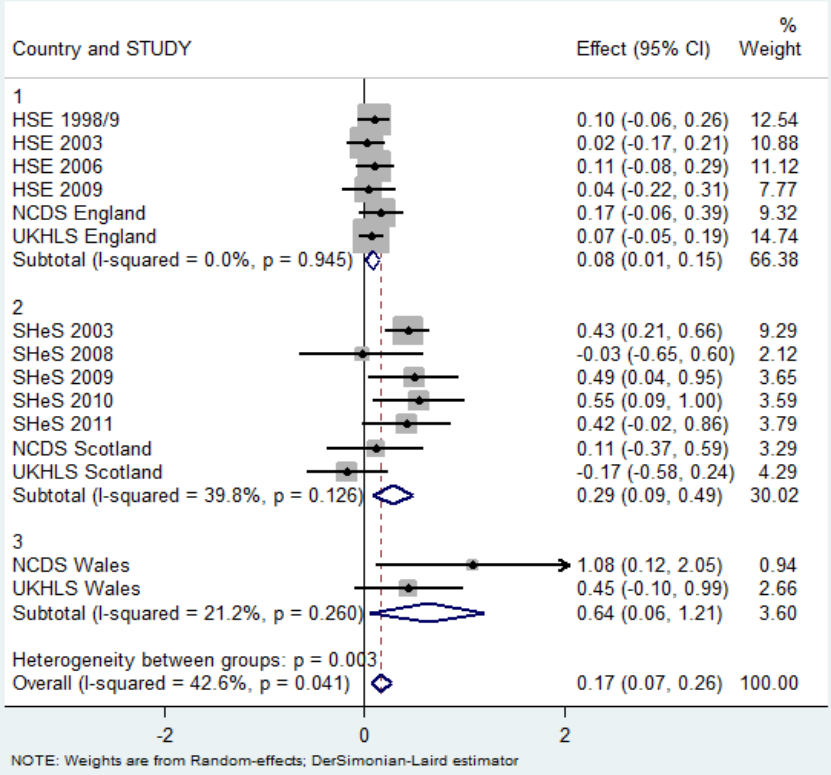


Figure 4.2: Unemployment and CRP across all studies, by year

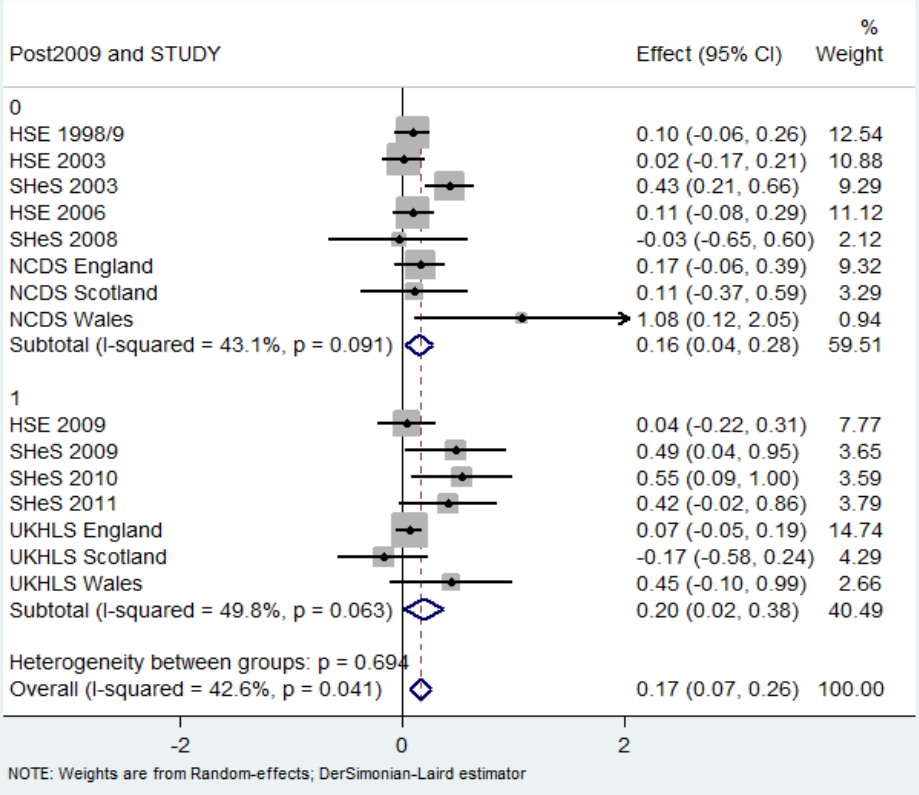


Figure 4.3: Unemployment and fibrinogen across all studies, by country

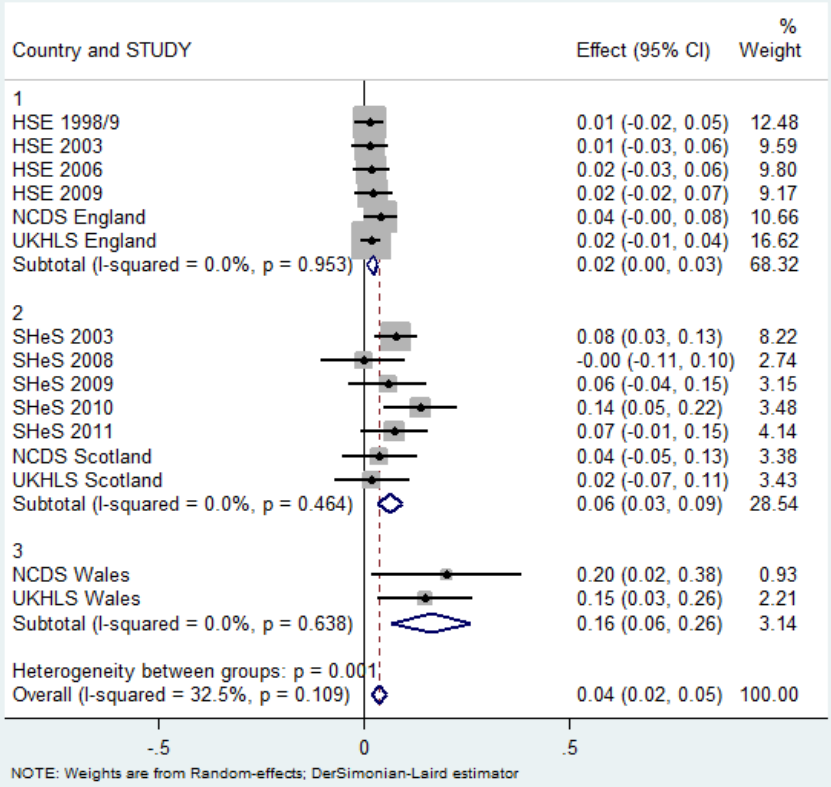


Figure 4.4: Unemployment and fibrinogen across all studies, by year

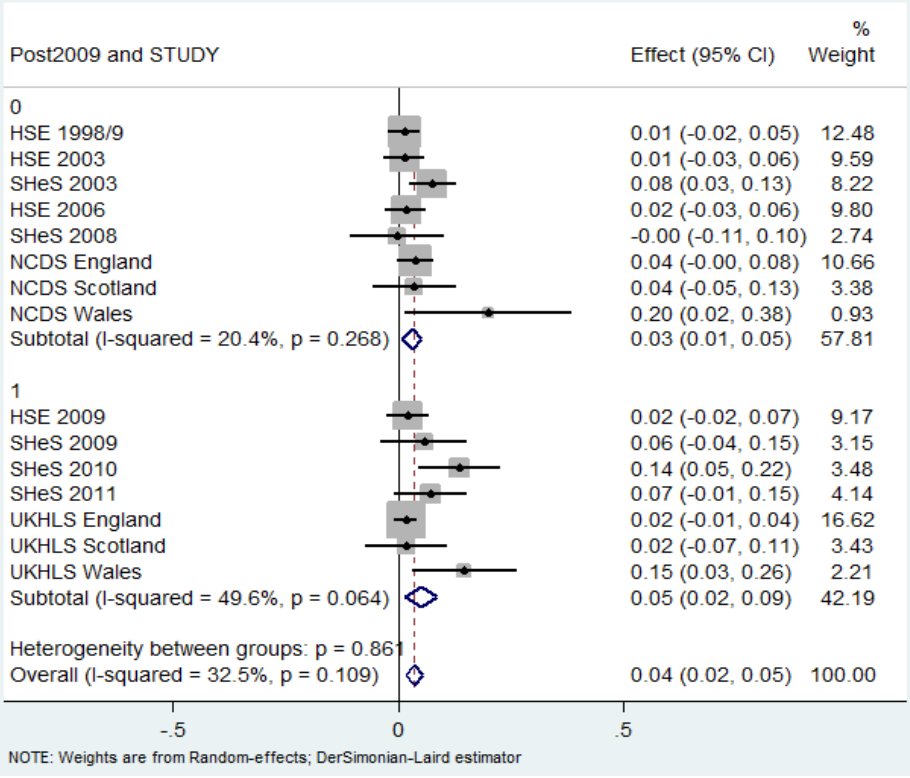


Figure 4.5: Unemployment and odds of CRP>3mg/L across all studies, by country

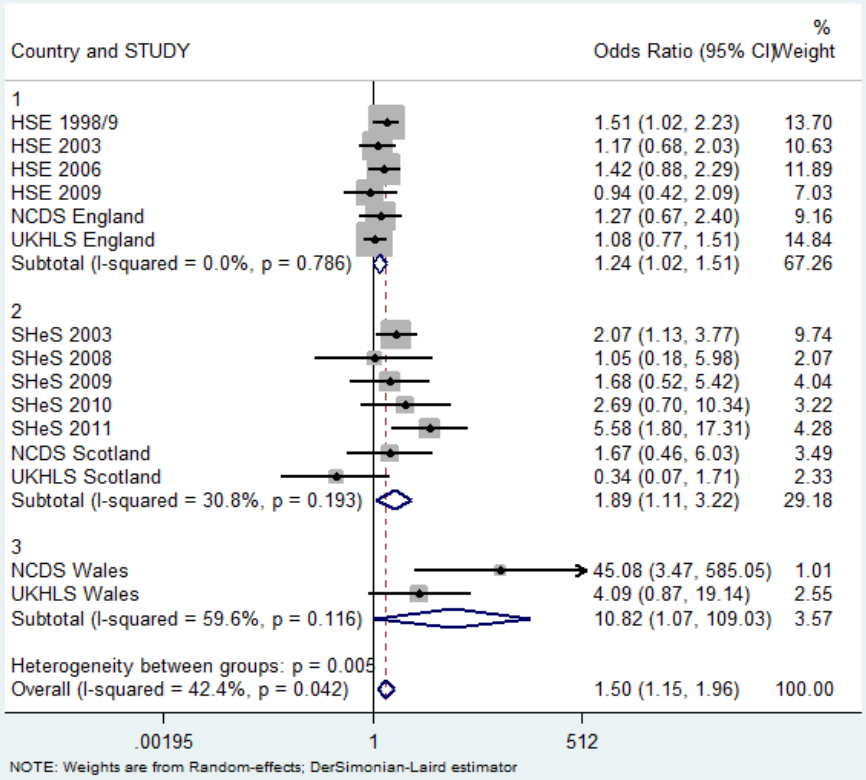
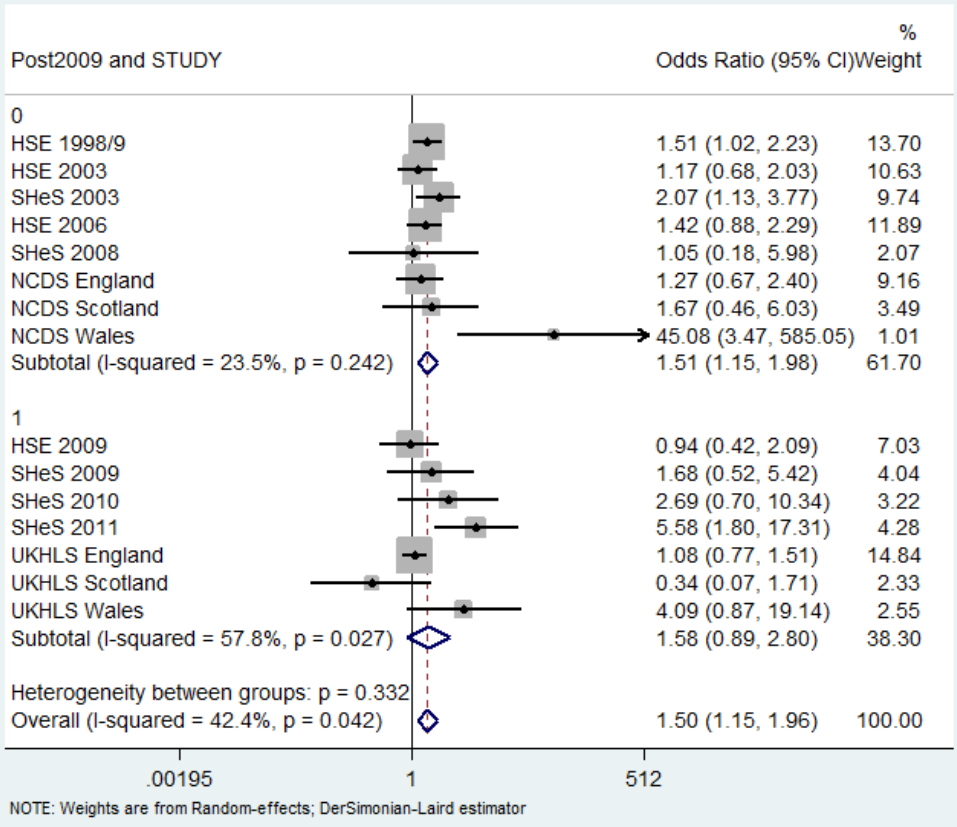


Figure 4.6: Unemployment and odds of CRP>3mg/L across all studies, by year



4.7 Overall Discussion

4.7.1 Discussion of meta-analytic results

The robust associations of all three inflammatory markers with unemployment in pooled analyses supports the hypothesis that, in a UK context, unemployment may influence systemic inflammation through stress pathways, independently of health behaviours, confounding by prior SEP, and pre-existing long-term illness. At the same time, the substantial heterogeneity across the studies suggests this association is strongly influenced by contextual factors.

The lack of a gender interaction in the pooled dataset is evidence against an interactive effect of unemployment and gender, given the numbers involved (610 unemployed men and 323 unemployed women in final CRP models). Similarly, the pooled analysis does not support an interactive relationship with age group.

Although all three inflammatory markers were significantly elevated in each country, the stratum-specific pooled estimates differed substantially between England, Scotland, and Wales. Indeed, country emerged as a much more important source of heterogeneity than year, despite considerable changes to both unemployment rates and the overall economic climate during the study period. In contrast to the literature comparing associations of unemployment and health within Europe, these country differences cannot be explained in terms of differential unemployment protection between welfare state regimes because unemployment protection is determined centrally at Westminster rather than being a devolved issue. As discussed in the HSE/SHeS analysis, this may instead point to the importance of accumulation processes if the length of a typical unemployment spell differs geographically, and could alternatively indicate that unemployment is a more stressful experience in areas where the background rate is high, since jobseekers will rationally perceive their prospects for re-employment as worse.

Pooling the Welsh components of NCDS and UKHLS samples allowed effects in Wales to be explored despite samples which would independently have been prohibitively small. While even the pooled

results for Wales are imprecise, the magnitude of associations is striking, and support the hypothesis that the strength of the relationship between unemployment and inflammation correlates positively with background unemployment rate and/or the average length of an unemployment spell in that area[211] [279]. Further research to investigate associations of unemployment and aspects of health related to inflammation in a Welsh context would be warranted.

Minimal within-stratum heterogeneity across English studies (I^2=0.0% for all three markers) suggests the relationship of unemployment and inflammation in England is not greatly affected by contextual factors such as changing economic climate. That the negative effects in the Southwest analyses were not seen in the pooled dataset suggests that finding in the HSE was a type 1 error. Considerable within-stratum heterogeneity was observed across Scottish studies, which was not accounted for by year and as yet remains unexplained.

That associations were slightly stronger in the period after 2009 than in the preceding decade does not support selection-based explanations for the worse health of jobseekers, which predict stronger associations in years when unemployment is low.

4.7.2 Fit with previous research

Only one cross-sectional study had previously been published looking at unemployment and inflammation, in that case indexed by IL-6, which reported an overall cross-sectional association among 225 Finnish men and women [213]. These findings therefore serve to confirm and extend results of that study using data from large scale, nationally representative UK studies. However, the small size and exclusive focus on Finland of Hintikka's study means appropriate comparisons cannot be made regarding the presence of gender, age or country modifications.

More generally, these results accord with the literature on systemic inflammation and other dimensions of socioeconomic marginalisation such as occupational social class[280] [274]. Like Hintikka's study, these results support a model on which unemployment, acting as an acute social

stressor, affects systemic inflammation via a psychosocial stress pathway. Given the association between systemic inflammation and cardiovascular disease, results are also consistent with the elevated mortality repeatedly observed among jobseekers.

4.7.3 Limitations

Aggregating all available study populations into a meta-analysis helped to overcome issues of power. Nevertheless, the considerable loss of participants between the initial and final samples in constituent samples meant concerns about resultant bias apply to the pooled analyses in addition to the individual analyses. Ideally this meta-analysis would have adjusted for a comparable measure of mental health, although it should be noted that in all three standalone analyses the addition of the mental health measure to otherwise fully-adjusted models made a minimal difference to associations.

4.8 Chapter Summary

This analysis found robust elevations in CRP, fibrinogen and odds of CRP>3mg/L among unemployed English, Scottish and Welsh men and women compared to employed counterparts in a time period spanning 1998-2012. However, there were substantial study effects: in contrast to NCDS and SHeS analyses, no significant associations were seen in UKHLS analyses in either England or Scotland. This variation remains unexplained. In the pooled dataset, strength of effects varied considerably by country, suggesting the relationship of unemployment with inflammation may be strongly influenced by environmental or contextual factors. In contrast, onset of the recession does not appear to have visibly affected associations compared to the preceding decade. If country differences in fact reflect life-course accumulation processes, they may indicate long-term or repeated unemployment as especially damaging to aspects of health related to inflammation. Alternatively, it could indicate that background unemployment rate modifies associations of current unemployment and this aspect of health independently of unemployment duration, possibly mediated through psychological processes to do with expectation of re-employment. Given the

substantial loss of data between those targeted for blood samples and usable measurements obtained for both the UKHLS and HSE/SHeS, it is possible that non-response bias could have affected results, whereas attrition bias could have affected results in NCDS analyses, which were also limited by a small number of unemployed participants. In the next chapter, investigation of the unemployment-inflammation association is extended to prospective analyses using NCDS and UKHLS data, to see whether any associations persist over time.

5 LONGITUDINAL ANALYSIS OF UNEMPLOYMENT AND INFLAMMATORY MARKERS

5.1 Chapter Overview

This chapter contains analyses relating to objective 3: investigation of longitudinal associations of past unemployment and inflammatory markers. Firstly, analyses using NCDS data, methods and results are presented for (1) total aggregated unemployment, (2) number of spells, (3) life period in which first unemployment occurred, and (4) time since last unemployment spell. Then UKHLS analyses, methods and results are presented for (1) total aggregated unemployment and (4) time since last unemployment spell. In the final section, both sets of results are discussed together with reference to initial hypotheses and the previous literature.

It was hypothesised that:

1. Inflammation at follow-up will increase with increasing total aggregated unemployment.
2. Inflammation at follow-up will increase with number of spells.
3. Inflammation will be more strongly associated with more recent unemployment.
4. Inflammation will be especially associated with unemployment spells earlier in life, indicating a sensitive period effect.

5.2 The NCDS

5.2.1 Methods

5.2.1.1 Analytic sample

Analysis was restricted to the 9363 participants present at the biomedical sweep when inflammatory markers were measured. Of these 9363, 1680 (17.9%) were missing CRP and 1689 (18.0%) were missing fibrinogen, and multiple imputation (M=20) was used to fill in missingness in covariates and inflammatory markers for these participants. Post-imputation, participants whose C-reactive protein exceeded 10mg/L were excluded from analysis, which meant the final sample varied from 9,042 to 9,067 between imputations.

5.2.1.2 Measures

5.2.1.2.1 Unemployment at age 44-45

The summary measures calculated from the updated activity histories dataset were:

1. Total aggregated unemployment in months since age 16. Since this was highly skewed, this was categorised into 0-6 months 7-12 months, 12-36 months, and >36 months.
2. Total number of unemployment spells since age 16. This was also highly skewed, and was categorised into 0, 1, 2, and 3+.
3. Timing of first unemployment, categorised as 16-21, 21-30, 30-40, 40+
4. Most recent unemployment, categorised as: current, within past 5 years, 5-15 years ago (age 30-40), 15-24 years ago (age 21-30), or >24 years ago (age 16-21).

5.2.1.2.2 Inflammatory markers at age 44-45

Systemic inflammation at age 44-45 was indexed by two markers: C-reactive protein in mg/L and fibrinogen in g/L. Both were log-transformed prior to analysis, and a dichotomous measure of CRP using a cut-point of 3mg/L was also used, since this is the level at which cardiovascular risk becomes

elevated. Participants whose C-reactive protein exceeded 10mg/L were excluded from analysis, to isolate systemic processes from acute infection.

5.2.1.2.3 Mental Health

Participants' mental health at age 16 was measured using the Rutter Scale. Following the procedure used by Clark and colleagues to adjust for early mental health in this dataset[252], five items from the parent version of the Rutter questionnaire indexing internalising (depression/anxiety) symptoms were drawn out and the square root of the subscale total calculated, and a further 9 items used to calculate an equivalent square root total of externalising symptoms (see methods chapter for the individual items). Mental health at 44-45 was indexed by log-transformed CIS-R score from the biomedical assessment.

Longstanding illness or disability

Also included as a component of relevant initial conditions at labour market entry was whether participants already had longstanding illness or disability, either reported by the parent or as noted during the physical examination component of the survey. Report of a longstanding illness at sweep 6 (age 42) was used in later models to examine whether any effects of unemployment on inflammation were explained by long-term illness.

5.2.1.2.4 Socioeconomic position

Socioeconomic position at labour market entry was measured by the housing tenure of participants' parents, and the occupational social class of the participants' father, when participants were aged 16. Father's social class and parental housing tenure from earlier in childhood, plus measures of overcrowding and reported financial difficulties in childhood, were used as auxiliary variables to impute these. For father's social class, participants living in households with no male head or a father not in employment during this period were included as a separate group. Socioeconomic

position at age 42 was indexed by participants' housing tenure and the occupational class of their current job or else the most recent job for which this information was available.

5.2.1.2.5 Health behaviours at age 42 and 44-45

Information on smoking and drinking also came from sweep 6. Smoking was assessed by self-report and classified as never smoker, ex-smoker, current (up to 10 per day), current (11-20 per day) and current (21+ per day). Frequency of alcohol consumption was assessed by self-report and classified as on most days, 2-3 days per week, less often, and non-drinkers. BMI was calculated from height and weight measured by a nurse at the biomedical sweep, and categorized using standard WHO classifications (<18.5, 18.5-24.9, 25-29.99, 30+).

5.2.1.3 Multiple Imputation

The four summary unemployment variables of total unemployment in months, number of spells, age at first unemployment and recentness of last unemployment at the time of biomedical assessment were included in imputation models along with log-transformed CRP and fibrinogen, all covariates, and a number of auxiliary variables such as malaise inventory items and SEP measures from earlier sweeps. As with models investigating Malaise Inventory at age 50, imputation models were restricted to participants who had activity history records which did not end prior to the biomedical sweep, to avoid the imputation model being informed by inconsistently calculated summary measures for participants with partial histories. This meant restricting models to the 11,259 participants with an activity history record who were present and gave information on current or former activities at the biomedical sweep, sweep 7 (two years later) or sweep 8 (five years later).

Prior to imputation, tests for interactive effects of gender and country were performed. Since interaction effects were not supported, interactions were not included in the imputation models and were not considered further.

5.2.1.4 Analyses

Linear regression was used to explore associations of lifetime unemployment with log-transformed CRP and fibrinogen, and logistic regressions to explore associations of lifetime unemployment with odds of CRP>3mg/L.

The first model adjusted for 'initial conditions': sex, physical health and SEP at 16, as well as country at outcome measurement. In subsequent models, five distinct pathways by which unemployment might impact later inflammation were explored. These were: long-term illness by age 42, SEP at 42, health behaviours at 42, current unemployment at age 44-45, and mental health at 44-45 as measured by log-transformed CIS-R score.

5.2.1.5 Sensitivity Analyses

The impact of potentially anti-inflammatory drugs was investigated by excluding participants prescribed statins, fibrates, corticosteroids or NSAIDs for any reason, hormone replacement therapy or oral contraceptives. The impact of considering time of day, season and processing time of blood samples was also explored.

Table 5.1: Characteristics of initial and final samples (NCDS)				
		Initial sample, unimputed (N=18558)	Present at biomedical sweep and excluding CRP>10mg/L: Unimputed (N=9133)	Present at biomedical sweep and excluding CRP>10mg/L: Imputed data (N=9,042)
		Mean	Mean	Mean
Mental health	Internalizing at 16	1.25*	1.12**	1.12
	Externalising at 16	1.34^{+}	1.13^{++}	1.19
	CIS-R at 44-45	3.40$^{\lozenge}$	3.35$^{\lozenge\lozenge}$	3.34
Inflammatory markers at 44-45	C-reactive protein	2.18°	1.65$^{\circ\circ}$	1.66
	Fibrinogen	2.95$^{\square}$	2.92$^{\square\square}$	2.93
		%	%	%
CRP>3mg/L at 44-45	No	33.9	68.0	83.2
	Yes	6.8	13.6	16.8
	Missing	59.3	18.4	-
Sex	Female	49.4	50.0	50.0
	Male	50.6	50.0	50.0
Longstanding illness/disability at 16	No	81.6	83.8	91.7
	Yes	8.0	7.5	8.3
	Missing	10.4	8.8	-
SEP in childhood: parental housing tenure	Owner-occupier	36.7	39.8	51.8
	Council rented	29.2	28.5	38.6
	Private rented/other	6.7	7.3	9.6
	Missing	27.5	24.4	-
SEP in childhood: father's occupational social class	Professional	3.6	4.2	4.8
	Managerial	13.4	15.0	16.7
	Skilled non-manual	6.4	6.9	7.7
	Skilled manual	29.6	30.7	33.7
	Semi-skilled	9.6	9.7	10.6
	Unskilled	3.6	3.1	3.4
	No male head/father not in work/forces	22.6	20.9	23.2
	Missing	11.2	9.5	-
Longstanding illness/disability at 42	No	43.4	69.0	71.4
	Yes	17.9	27.8	28.6
	Missing	38.7	3.1	-
Housing tenure at 42	Owns outright	5.1	7.9	8.2
	Buying (mortgage)	44.2	72.5	75.0
	Council rented	4.5	6.5	6.7
	Pvt renting/other	7.3	9.7	10.1
	Missing	38.9	3.4	-
Occupational social class at 42 from current or last employment	Professional	3.0	5.2	5.4
	Managerial	21.4	35.2	36.4
	Skilled non-manual	13.5	21.2	21.9
	Skilled manual	12.2	18.7	19.5
	Semi-skilled	8.5	12.7	13.2
	Unskilled	2.5	3.4	3.6
	Missing	39.1	3.6	-
Smoking at 42	Never smoker	27.3	44.4	45.8
	Ex-smoker	15.5	24.9	25.6
	Current, up to 10/day	7.0	10.7	11.1
	Current, 11-20/day	8.7	12.9	13.4

	Current, 21+/day	2.8	3.9	4.1
	Missing	38.7	3.2	-
Drinking frequency at 42	Most days	12.1	19.5	20.2
	2-3 days/week	19.8	32.1	33.2
	Less often	26.1	40.6	41.7
	Non-drinker	3.3	4.8	4.9
	Missing	38.7	3.1	-
BMI at 44-45	18.5-24.9	16.8	33.7	34.4
	25.0-29.9	20.5	40.9	41.5
	30.0-34.9	8.4	16.5	16.7
	>35.0	3.7	6.8	6.8
	<18.5	0.3	0.5	0.6
	Missing	50.4	1.6	-
Country of residence at 44-45	England	52.3	83.1	85.8
	Scotland	3.4	5.0	9.1
	Wales	5.8	8.9	5.1
	Missing	38.5	3.1	-
Anti-inflammatory medications, oral contraceptives, or HRT	No	41.3	82.3	82.4
	Yes	9.2	17.8	17.6
	Missing	49.5	0.0	-
*Based on 12271 obs **Based on 7165 obs $^{+}$Based on 12138 obs $^{++}$Based on 7171 obs $^{\lozenge}$Based on 9297 obs $^{\lozenge\lozenge}$Based on 9066 obs $^{\circ}$Based on 7692 obs $^{\circ\circ}$Based on 7453 obs $^{\square}$Based on 7683 obs $^{\square\square}$Based on 7445 obs				

Table 5.2: Unemployment summary variables, final sample (unimputed data)

		(%)
Total unemployment (months) age 16-50	Never unemployed	64.1
	Up to 6 months	16.2
	6-12 months	6.8
	13-36 months	7.5
	37+ months	5.4
Number of unemployment spells	Never unemployed	64.1
	1	21.5
	2	7.6
	3 or more	6.7
Timing of first unemployment	Never unemployed	64.1
	16-21	12.3
	21-30	15.2
	30-40	6.3
	>=40	2.1
Timing of most recent unemployment	Never unemployed	64.1
	Current	1.6
	Ended <5 years ago	4.3
	Ended 5-15 years ago	9.8
	Ended 15-24 years ago	13.8
	Ended >24 years ago	6.3

Table 5.3: Association of unemployment summary variables with inflammatory markers at age 45, NCDS (N=9042)

*Initial Conditions: *Sex + internalising and externalising symptoms + longterm illness + SEP at 16, plus country at 44-45*

Reference group is participants never unemployed

	Log-transformed C-reactive protein				Odds of CRP>3mg/L				Log-transformed fibrinogen			
TOTAL AGGREGATED UNEMPLOYMENT, 16-45												
		Coeff	CI	p		Coeff	CI	p		Coeff	CI	p
Adjustment: Sex and country	Up to 6 months	-0.01	-0.08,0.06	0.77	Up to 6 months	0.96	0.81,1.14	0.66	Up to 6 months	0.00	-0.01,0.01	0.66
	6-12 months	-0.07	-0.17,0.03	0.16	6-12 months	1.04	0.81,1.32	0.76	6-12 months	0.00	-0.02,0.01	0.75
	1-3 years	0.09	-0.00,0.19	0.05	1-3 years	1.17	0.93,1.48	0.17	1-3 years	0.03	0.01,0.05	0.001
	> 3 years	0.16	0.04,0.27	0.01	> 3 years	1.45	1.13,1.87	0.004	> 3 years	0.05	0.03,0.07	<0.001
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Initial conditions	Up to 6 months	0.00	-0.07,0.06	0.89	Up to 6 months	0.97	0.82,1.16	0.76	Up to 6 months	0.00	-0.01,0.02	0.62
	6-12 months	-0.08	-0.18,0.02	0.13	6-12 months	1.03	0.81,1.31	0.81	6-12 months	0.00	-0.02,0.01	0.66
	1-3 years	0.06	-0.04,0.15	0.23	1-3 years	1.10	0.87,1.38	0.43	1-3 years	0.02	0.01,0.04	0.01
	> 3 years	0.06	-0.05,0.18	0.27	> 3 years	1.25	0.97,1.62	0.08	> 3 years	0.03	0.01,0.05	0.001
NUMBER OF UNEMPLOYMENT SPELLS, 16-45												
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Sex and country	1	0.03	-0.03,0.09	0.37	1	1.07	0.92,1.24	0.41	1	0.01	-0.00,0.02	0.08
	2	-0.02	-0.11,0.08	0.75	2	1.12	0.89,1.41	0.34	2	0.02	-0.00,0.03	0.05
	3 or more	0.06	-0.04,0.16	0.25	3 or more	1.12	0.88,1.43	0.37	3 or more	0.02	0.01,0.04	0.01
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Initial conditions	1	0.01	-0.05,0.07	0.63	1	1.04	0.90,1.22	0.57	1	0.01	-0.00,0.02	0.20
	2	-0.03	-0.12,0.06	0.53	2	1.09	0.86,1.37	0.48	2	0.01	-0.00,0.03	0.11
	3 or more	0.01	-0.09,0.11	0.88	3 or more	1.03	0.80,1.31	0.83	3 or more	0.01	-0.00,0.03	0.13

Table 5.4: Continued: Association of unemployment summary variables with inflammatory markers at age 45, NCDS (N=9042)

*Initial Conditions: *Sex + internalising and externalising symptoms + longterm illness + SEP at 16, plus country at 44-45*

Reference group is participants never unemployed

	Log-transformed C-reactive protein				Odds of CRP>3mg/L				Log-transformed fibrinogen			
AGE AT FIRST UNEMPLOYMENT												
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Sex and country	16-21	0.05	-0.03,0.13	0.24	16-21	1.10	0.91,1.34	0.32	16-21	0.02	0.01,0.03	0.01
	21-30	-0.04	-0.11,0.03	0.23	21-30	0.97	0.81,1.16	0.72	21-30	0.00	-0.01,0.01	0.83
	30-40	0.11	0.00,0.21	0.05	30-40	1.31	1.02,1.68	0.03	30-40	0.04	0.02,0.06	<0.001
	>40	0.12	-0.05,0.29	0.16	>40	1.21	0.80,1.83	0.38	>40	0.03	-0.00,0.06	0.05
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Initial conditions	16-21	0.01	-0.07,0.09	0.81	16-21	1.04	0.85,1.26	0.71	16-21	0.01	-0.00,0.02	0.11
	21-30	-0.04	-0.11,0.03	0.26	21-30	0.97	0.81,1.16	0.77	21-30	0.00	-0.01,0.01	0.85
	30-40	0.07	-0.04,0.17	0.22	30-40	1.23	0.96,1.58	0.11	30-40	0.03	0.01,0.05	0.002
	>40	0.10	-0.06,0.27	0.23	>40	1.16	0.76,1.76	0.49	>40	0.03	-0.00,0.06	0.10
RECENTNESS OF LAST UNEMPLOYMENT												
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Sex and country	Current	0.22	0.02,0.42	0.03	Current	1.70	1.11,2.62	0.02	Current	0.07	0.03,0.10	<0.001
	<5yrs ago	0.11	-0.02,0.24	0.10	<5yrs ago	1.27	0.92,1.74	0.14	<5yrs ago	0.03	0.00,0.05	0.03
	5-15 yrs ago	0.06	-0.03,0.15	0.20	5-15 yrs ago	1.19	0.96,1.49	0.11	5-15 yrs ago	0.02	0.01,0.04	0.01
	15-24 yrs ago	-0.08	-0.15,-0.01	0.04	15-24 yrs ago	0.91	0.75,1.11	0.37	15-24 yrs ago	-0.01	-0.02,0.01	0.43
	24-29 yrs ago	0.01	-0.10,0.12	0.83	24-29 yrs ago	0.95	0.72,1.25	0.69	24-29 yrs ago	0.01	-0.01,0.02	0.46
		Coeff	CI	p		OR	CI	p		Coeff	CI	p
Adjustment: Initial conditions	Current	0.17	-0.03,0.36	0.10	Current	1.57	1.02,2.41	0.04	Current	0.06	0.02,0.09	0.001
	<5yrs ago	0.08	-0.05,0.21	0.23	<5yrs ago	1.21	0.88,1.66	0.24	<5yrs ago	0.02	-0.00,0.04	0.09
	5-15 yrs ago	0.03	-0.06,0.12	0.50	5-15 yrs ago	1.15	0.92,1.43	0.22	5-15 yrs ago	0.02	0.00,0.03	0.04
	15-24 yrs ago	-0.07	-0.15,0.00	0.06	15-24 yrs ago	0.93	0.76,1.13	0.45	15-24 yrs ago	0.00	-0.02,0.01	0.45
	24-29 yrs ago	-0.01	-0.11,0.10	0.91	24-29 yrs ago	0.92	0.70,1.21	0.55	24-29 yrs ago	0.00	-0.01,0.02	0.73

Table 5.4: Association of aggregated unemployment and age at first unemployment with fibrinogen at 45, NCDS
Reference group for all analyses is participants never unemployed

ADJUSTMENT LEVEL	Total aggregated unemployment				Age at First Unemployment			
Sex and country		Coeff	CI	p		Coeff	CI	p
	Up to 6 months	0.00	-0.01,0.01	0.66	16-21	0.02	0.01,0.03	0.01
	6-12 months	0.00	-0.02,0.01	0.75	21-30	0.00	-0.01,0.01	0.83
	1-3 years	0.03	0.01,0.05	0.001	30-40	0.04	0.02,0.06	<0.001
	> 3 years	0.05	0.03,0.07	<0.001	>40	0.03	-0.00,0.06	0.05
Initial conditions		Coeff	CI	p		Coeff	CI	p
	Up to 6 months	0.00	-0.01,0.02	0.62	16-21	0.01	-0.00,0.02	0.11
	6-12 months	0.00	-0.02,0.01	0.66	21-30	0.00	-0.01,0.01	0.85
	1-3 years	0.02	0.01,0.04	0.01	30-40	0.03	0.01,0.05	0.002
	> 3 years	0.03	0.01,0.05	0.001	>40	0.03	-0.00,0.06	0.10
SEP pathway: Initial conditions + country, SEP at 45		Coeff	CI	p		Coeff	CI	P
	Up to 6 months	0.00	-0.01,0.02	0.63	16-21	0.01	-0.01,0.02	0.37
	6-12 months	-0.01	-0.02,0.01	0.51	21-30	0.00	-0.02,0.01	0.45
	1-3 years	0.02	-0.00,0.03	0.07	30-40	0.02	0.00,0.04	0.02
	> 3 years	0.01	-0.01,0.03	0.23	>40	0.02	-0.01,0.05	0.19
Physical health pathway: Initial conditions + country, physical health at 45		Coeff	CI	p		Coeff	CI	P
	Up to 6 months	0.00	-0.01,0.01	0.70	16-21	0.01	-0.00,0.02	0.16
	6-12 months	0.00	-0.02,0.01	0.60	21-30	0.00	-0.02,0.01	0.74
	1-3 years	0.02	0.00,0.04	0.01	30-40	0.03	0.01,0.05	0.003
	> 3 years	0.03	0.01,0.05	0.003	>40	0.02	-0.01,0.06	0.11
Mental health pathway: Initial conditions + country, CIS-R at 45		Coeff	CI	p		Coeff	CI	P
	Up to 6 months	0.00	-0.01,0.01	0.69	16-21	0.01	-0.00,0.02	0.14
	6-12 months	0.00	-0.02,0.01	0.60	21-30	0.00	-0.01,0.01	0.76
	1-3 years	0.02	0.00,0.04	0.01	30-40	0.03	0.01,0.05	0.002
	> 3 years	0.03	0.01,0.05	0.001	>40	0.03	-0.01,0.06	0.10
Current unemployment pathway: Initial conditions + country and current unemployment at 45		Coeff	CI	p		Coeff	CI	P
	Up to 6 months	0.00	-0.01,0.01	0.73	16-21	0.01	-0.00,0.02	0.16
	6-12 months	0.00	-0.02,0.01	0.59	21-30	0.00	-0.01,0.01	0.78
	1-3 years	0.02	0.00,0.04	0.01	30-40	0.03	0.01,0.05	0.003
	> 3 years	0.03	0.01,0.05	0.007	>40	0.01	-0.02,0.05	0.41
Health behaviours pathway: Initial conditions + country, health behav's at 42/45		Coeff	CI	p		Coeff	CI	P
	Up to 6 months	0.00	-0.01,0.01	0.72	16-21	0.00	-0.01,0.02	0.54
	6-12 months	0.00	-0.02,0.01	0.65	21-30	0.00	-0.01,0.01	0.87
	1-3 years	0.02	0.00,0.03	0.04	30-40	0.02	0.00,0.04	0.04
	> 3 years	0.02	-0.00,0.04	0.09	>40	0.02	-0.01,0.05	0.26
Full model: Initial Conditions+ country, SEP, physical health, CIS-R, current unempl., health behav's at 42/45		Coeff	CI	p		Coeff	CI	P
	Up to 6 months	0.00	-0.01,0.01	0.91	16-21	0.00	-0.01,0.01	0.94
	6-12 months	-0.01	-0.02,0.01	0.49	21-30	0.00	-0.01,0.01	0.86
	1-3 years	0.01	-0.00,0.03	0.11	30-40	0.01	-0.00,0.03	0.11
	> 3 years	0.00	-0.02,0.02	0.74	>40	0.00	-0.03,0.03	0.87

Table 5.5: Association of recentness of last unemployment with inflammatory markers at age 45, NCDS (N=8670)

*Initial Conditions: *Sex + internalising and externalising symptoms + longterm illness + SEP at 16, plus country at 44-45*

*Reference group is participants never unemployed. Participants currently sick/disabled excluded

		Log-transformed C-reactive protein			Odds of CRP>3mg/L			Log-transformed fibrinogen		
		Coeff	CI	p	OR	CI	p	Coeff	CI	P
SEP pathway: Initial conditions + country, SEP at 45	Current	0.09	-0.10,0.29	0.35	1.34	0.87,2.07	0.18	0.04	0.01,0.08	0.02
	Ended age 40-45 (<5yrs ago)	0.04	-0.09,0.17	0.56	1.11	0.80,1.53	0.54	0.01	-0.01,0.03	0.38
	Ended age 30-40 (5-15 yrs ago)	0.00	-0.08,0.09	0.92	1.1	0.88,1.37	0.41	0.01	-0.01,0.03	0.17
	Ended age 21-30 (15-24 yrs ago)	-0.08	-0.15,-0.00	0.04	0.92	0.76,1.12	0.41	-0.01	-0.02,0.01	0.40
		-0.01	-0.12,0.09	0.80	0.9	0.68,1.20	0.48	0.00	-0.02,0.02	0.85
		Coeff	CI	p	OR	CI	p	Coeff	CI	p
Physical health pathway: Initial conditions + country, physical health at 45	Current	0.16	-0.04,0.35	0.12	1.54	1.00,2.36	0.05	0.06	0.02,0.09	0.002
	Ended age 40-45 (<5yrs ago)	0.07	-0.06,0.20	0.28	1.19	0.86,1.64	0.29	0.02	-0.00,0.04	0.11
	Ended age 30-40 (5-15 yrs ago)	0.02	-0.07,0.11	0.62	1.13	0.90,1.40	0.29	0.02	-0.00,0.03	0.06
	Ended age 21-30 (15-24 yrs ago)	-0.08	-0.15,-0.00	0.04	0.92	0.75,1.12	0.39	-0.01	-0.02,0.01	0.43
	Ended age 16-21 (24-29 yrs ago)	-0.01	-0.12,0.10	0.85	0.91	0.69,1.20	0.51	0.00	-0.01,0.02	0.77
		Coeff	CI	p	OR	CI	p	Coeff	CI	p
Mental health pathway: Initial conditions + country, CIS-R at 45	Current	0.15	-0.04,0.35	0.12	1.55	1.01,2.38	0.046	0.06	0.02,0.09	0.001
	Ended age 40-45 (<5yrs ago)	0.07	-0.06,0.20	0.29	1.19	0.87,1.64	0.27	0.02	-0.00,0.04	0.10
	Ended age 30-40 (5-15 yrs ago)	0.02	-0.06,0.11	0.59	1.14	0.91,1.42	0.25	0.02	0.00,0.03	0.05
	Ended age 21-30 (15-24 yrs ago)	-0.08	-0.15,-0.00	0.04	0.92	0.76,1.12	0.41	-0.01	-0.02,0.01	0.47
	Ended age 16-21 (24-29 yrs ago)	-0.01	-0.12,0.10	0.84	0.91	0.69,1.21	0.52	0.00	-0.01,0.02	0.75
		Coeff	CI	p	OR	CI	p	Coeff	CI	p
Health behaviours pathway: Initial conditions + country, health behav's at 42/45	Current	0.21	0.03,0.39	0.02	1.76	1.12,2.76	0.01	0.05	0.02,0.09	0.002
	Ended age 40-45 (<5yrs ago)	0.05	-0.07,0.17	0.43	1.11	0.78,1.58	0.55	0.01	-0.01,0.03	0.39
	Ended age 30-40 (5-15 yrs ago)	-0.02	-0.10,0.06	0.64	1.02	0.81,1.30	0.86	0.01	-0.01,0.02	0.42
	Ended age 21-30 (15-24 yrs ago)	-0.06	-0.13,0.01	0.09	0.93	0.75,1.14	0.48	0.00	-0.02,0.01	0.68
	Ended age 16-21 (24-29 yrs ago)	-0.03	-0.13,0.07	0.54	0.84	0.63,1.14	0.26	0.00	-0.02,0.02	1.00
		Coeff	CI	p	OR	CI	p	Coeff	CI	p
Full model: Initial Conditions+ country, SEP, physical health, CIS-R, health behav's at 42/45	Current	0.18	0.00,0.36	0.046	1.63	1.04,2.57	0.03	0.05	0.02,0.08	0.004
	Ended age 40-45 (<5yrs ago)	0.03	-0.09,0.15	0.60	1.08	0.76,1.54	0.67	0.01	-0.02,0.03	0.54
	Ended age 30-40 (5-15 yrs ago)	-0.03	-0.11,0.05	0.45	1.00	0.79,1.27	1.00	0.01	-0.01,0.02	0.54
	Ended age 21-30 (15-24 yrs ago)	-0.06	-0.13,0.00	0.06	0.92	0.75,1.14	0.45	0.00	-0.02,0.01	0.62
	Ended age 16-21 (24-29 yrs ago)	-0.04	-0.14,0.06	0.46	0.84	0.62,1.13	0.25	0.00	-0.02,0.02	0.94

5.2.2 Results

Descriptive characteristics of initial and final samples are shown in Table 5.1. Participants still present at the biomedical sweep were more likely to be female and less likely to have had a longterm illness at age 16 ($p<0.001$). They were of more advantaged SEP at 16 as measured by both father's RGSC and housing tenure (both $p<0.001$), less likely to live in England ($p=0.01$), and had fewer internalising and externalising symptoms at 16 (both $p<0.001$). The final sample was therefore selected for favourable socioeconomic position, physical and mental health at labour market entry.

5.2.2.1 Crude and Initial Conditions models

Table 5.3 shows that adjusted for sex and country, total aggregated unemployment between ages 16-45 was significantly associated with elevations in CRP and fibrinogen for the top two groups of 1-3 years and 3+ years unemployment. Attenuation of effect sizes occurred with adjustment for initial conditions; for CRP outcomes initially strong effects for the >3 years group reduced substantially and became non-significant, such that only for fibrinogen did an apparent stepwise relationship remain after adjustment for initial conditions. Adjusted for sex and country, fibrinogen was significantly higher for participants who had experienced 2 or 3+ spells of unemployment, but no significant associations were seen for this exposure and CRP outcomes, and the elevations in fibrinogen were not robust to adjustment for initial conditions. For age at first unemployment, adjusted for sex and country the only significant elevations were among participants whose first unemployment had fallen between ages 30 and 40, for whom all three markers were significantly raised. However, only the association with fibrinogen remained after adjustment for initial conditions (coeff: 0.03, $p=0.002$). In sex- and country-adjusted models of recentness of last unemployment, CRP outcomes were raised for current but no categories of past unemployment, and fibrinogen was raised for current unemployment, unemployment ending <5 years ago, and unemployment ending 5-10 years ago. After adjustment for initial conditions, odds of CRP>3mg/L and fibrinogen were significantly raised for currently unemployed participants, as was fibrinogen for participants last unemployed 5-

10 years ago. The other associations, including log-transformed CRP for currently unemployed participants (coeff: 0.17, p=0.10) were not robust.

As a result of initial conditions models, the only analyses taken forward were: analyses of total aggregated unemployment and age at first unemployment in the case of fibrinogen, and recentness of last unemployment for all three markers.

5.2.2.2 Pathways

Mediation models (Table 5.4) showed that associations of total aggregated unemployment with fibrinogen were largely accounted for by SEP and health behaviours at age 42, while physical and mental health and current unemployment did not explain the association in this population. The same pattern was seen for age at first unemployment (Table 5.4). For both exposures, full adjustment for SEP, physical and mental health, current unemployment and health behaviours at 42/45 fully explained associations.

For recentness of last unemployment, a very different pattern was seen (Table 5.5). For all three inflammatory outcomes, adjustment for SEP at 42 once again produced substantial attenuation, and physical and mental health again made little difference. However, for the currently unemployed group addition of health behaviours caused effect sizes for both CRP outcomes to increase substantially and become significant, indicating that health behaviours had been working as a suppressor. A more detailed analysis (Table 5.6) indicated this was driven by BMI. Consistent with a BMI distribution at the biomedical sweep of 33.8% healthy weight, 43.1% overweight, and 22.9% obese or super-obese for employed participants, compared to 44.1% healthy weight, 35.6% overweight and 19.5% obese or super-obese for unemployed participants in the final sample. When health behaviours were taken into account alongside SEP and physical and mental health, a robust and substantial association of current unemployment with all three inflammatory outcomes remained.

Table 5.6: Attenuation with addition of individual health behaviours to initial conditions models: current unemployment (NCDS)

ADJUSTMENT LEVEL	Log-transformed CRP			Odds of CRP>3mg/L			Log-transformed Fibrinogen		
	Coeff	CI	P	OR	CI	p	Coeff	CI	p
Initial conditions	0.17	-0.03,0.36	0.10	1.57	1.02,2.41	0.04	0.06	0.02,0.09	0.001
+ smoking	0.12	-0.08,0.31	0.24	1.45	0.94,2.24	0.09	0.04	0.01,0.08	0.02
+ alcohol consumption	0.17	-0.03,0.36	0.09	1.59	1.03,2.44	0.04	0.06	0.02,0.09	0.001
+ BMI	0.27	0.09,0.45	0.004	1.95	1.24,3.06	0.004	0.07	0.03,0.10	<0.001

An additional analysis (Table 5.7) added health behaviours to the initial conditions models for the other summary variables, and confirmed that this effect was restricted to current unemployment.

Table 5.7: Addition of health behaviours to initial conditions models for CRP outcomes (NCDS)
Reference group for all analyses is participants never unemployed

INITIAL CONDITIONS + HEALTH BEHAVIOURS	Log-transformed CRP				Odds of CRP>3mg/L			
TOTAL AGGREGATED UNEMPLOYMENT		Coeff	CI	P		OR	CI	p
	Up to 6 months	-0.02	-0.08,0.04	0.57	16-21	0.93	0.78,1.12	0.47
	6-12 months	-0.07	-0.16,0.02	0.15	21-30	0.99	0.76,1.30	0.95
	1-3 years	0.04	-0.04,0.13	0.35	30-40	1.07	0.83,1.37	0.61
	> 3 years	0.02	-0.09,0.13	0.71	>40	1.13	0.85,1.49	0.40
NUMBER OF SPELLS		Coeff	CI	P		Coeff	CI	p
	1	0.00	-0.05,0.06	0.95	1	1.00	0.85,1.18	0.96
	2	-0.04	-0.13,0.04	0.31	2	1.02	0.79,1.31	0.89
	3+	-0.01	-0.10,0.09	0.90	3+	0.97	0.74,1.27	0.82
AGE AT FIRST UNEMPLOYMENT	16-21	-0.02	-0.09,0.05	0.56	16-21	0.95	0.77,1.17	0.64
	21-30	-0.02	-0.08,0.04	0.52	21-30	0.99	0.81,1.20	0.89
	30-40	0.02	-0.08,0.11	0.71	30-40	1.11	0.85,1.45	0.46
	>40	0.06	-0.09,0.22	0.41	>40	1.08	0.69,1.71	0.73

5.2.2.3 Sensitivity Analyses

Sensitivity analyses were then conducted, adjusted for initial conditions. Excluding participants taking anti-inflammatory medications, oral contraceptives or HRT did not appear to substantially change results (Table 5.8). A slight increase in CRP associations for the top group of total unemployment brought these associations slightly more in line with fibrinogen, although that association also strengthened. A direct comparison was however not possible because the drop in power resulting from exclusion of 17.6% of participants meant a drop in precision of estimates. Taking into account processing time, time of day and season of blood samples also did not affect conclusions.

Table 5.8: Initial conditions models, participants taking anti-inflammatory medications excluded, NCDS (N=7452)

	Log-transformed CRP			Odds of CRP>3mg/L			Log-transformed Fibrinogen		
TOTAL UNEMPLOYMENT	Coeff	CI	p	OR	CI	p	Coeff	CI	p
Up to 6 months	0.01	-0.07,0.08	0.86	1.04	0.85,1.26	0.71	0.00	-0.01,0.02	0.51
6-12 months	-0.09	-0.20,0.02	0.10	0.93	0.69,1.25	0.65	-0.01	-0.03,0.01	0.38
1-3 years	0.03	-0.07,0.13	0.52	1.01	0.77,1.34	0.92	0.02	0.00,0.04	0.04
> 3 years	0.08	-0.05,0.20	0.21	1.33	1.00,1.77	0.05	0.04	0.02,0.06	0.001
NUMBER OF SPELLS	Coeff	CI	p	OR	CI	p	Coeff	CI	p
1	0.02	-0.05,0.08	0.60	1.05	0.88,1.26	0.58	0.01	-0.01,0.02	0.37
2	-0.02	-0.12,0.09	0.76	1.18	0.91,1.54	0.21	0.02	-0.00,0.04	0.06
3+	-0.02	-0.13,0.09	0.72	0.92	0.69,1.23	0.58	0.01	-0.01,0.03	0.20
AGE AT FIRST UNEMPLOYMENT	Coeff	CI	p	OR	CI	p	Coeff	CI	p
16-21	0.00	-0.09,0.08	0.96	1.01	0.81,1.27	0.92	0.01	-0.00,0.03	0.09
21-30	-0.02	-0.10,0.05	0.55	1.00	0.82,1.23	0.98	0.00	-0.02,0.01	0.72
30-40	0.06	-0.05,0.18	0.29	1.23	0.92,1.65	0.17	0.03	0.01,0.05	0.005
>40	0.06	-0.13,0.24	0.55	1.15	0.70,1.89	0.58	0.02	-0.01,0.06	0.17
RECENTNESS OF LAST UNEMPLOYMENT (N=7263)	Coeff	CI	p	OR	CI	p	Coeff	CI	p
Current	0.14	-0.08,0.35	0.21	1.60	0.99,2.60	0.06	0.05	0.01,0.09	0.01
Ended age 40-45 (<5yrs ago)	0.03	-0.11,0.16	0.68	1.01	0.69,1.49	0.95	0.01	-0.01,0.04	0.28
Ended age 30-40 (5-15 yrs ago)	0.03	-0.06,0.13	0.49	1.16	0.90,1.51	0.25	0.02	-0.00,0.04	0.05
Ended age 21-30 (15-24 yrs ago)	-0.07	-0.14,0.01	0.10	0.95	0.76,1.19	0.67	0.00	-0.02,0.01	0.70
Ended age 16-21 (24-29 yrs ago)	0.00	-0.12,0.11	0.94	0.88	0.63,1.23	0.45	0.00	-0.02,0.02	0.75

5.3 Analyses using Understanding Society

5.3.1 Methods

5.3.1.1 Analytic sample

While the BHPS began in 1991, a high rate of attrition means that only 1625 participants present and of working age in 1991 were still present as of the biomedical component of UKHLS wave 3. Since these numbers are clearly insufficient for meaningful analyses, this longitudinal component focused on a 10-year exposure period between 2001 and 2011, which allowed analysis of 2865 participants.

This initial sample used for imputation models contained all members of the BHPS component of the UKHLS who were present in 2001 who would later be eligible for inclusion in the UKHLS nurse visit in 2011 (N=13885). Multiple imputation using chained equations was used to fill in missing data within this baseline sample. Analysis models were restricted, post-imputation, to participants who had been of working age (15-64) in 2001, and longitudinal weights applied to further account for non-random attrition between baseline and outcome. Because participants who had skipped waves between 2001 and 2011 were assigned longitudinal weights of zero, analysis models were effectively restricted to participants continuously present across the ten-year period. Participants whose CRP had exceeded 10mg/L were excluded, resulting in a final sample size of 2754 in unimputed data and which varied from 2685 and 2714 between imputations.

5.3.1.2 Measures

5.3.1.2.1 Unemployment in 2011

For this study population, past unemployment in 2011 was operationalised in the following ways: total months of unemployment over the study period (categorised into never unemployed, 1-6 months, 7-12 months, 13-24 months, >24 months) and recentness of the last unemployment spell (current, since 2006, 2001-2006, or not unemployed during the 10-year period). In contrast to analyses using the 1958 Birth Cohort employment history information was imputed (although not used in analysis models). This meant it was not possible to examine the number of spells in addition

to total months of unemployment. Also in contrast to the 1958 Birth Cohort, it was not possible to study the impact of the timing of a person's first experience of unemployment because full employment histories since labour market entry were not available for these participants.

As described in more detail in the methods chapter, summary unemployment variables were derived from considering all current and past spells ever reported by BHPS participants between 2001 and 2011. Since the nurse visit took place five months after the mainstage interview in 2011, the first five months of employment history information from the 2012 wave (UKHLS W4) was also taken into account when deriving measures of past and current unemployment as of the nurse interview itself, and treated as an extension of the 2011 wave.

5.3.1.2.2 Inflammatory markers

Systemic inflammation was indexed by C-reactive protein and fibrinogen. As with other analyses, both CRP and fibrinogen were log-transformed prior to analysis and CRP was also studied as a dichotomous outcome using the standard cut-point of 3mg/L. Participants with CRP>10mg/L were excluded from both CRP and fibrinogen analyses post-imputation to isolate systemic inflammation from acute inflammation associated with current infection, leading to a final sample size of about 2704 (this varied slightly between imputations). Sensitivity analyses investigated the impact of excluding participants taking medications which would affect inflammation or fibrinogen specifically.

5.3.1.2.3 Covariates at baseline and outcome

As with longitudinal analyses using the 1958 Cohort study, the analytic strategy involved adjustment for 'initial conditions' at baseline and further exploration of mediating pathways. Initial conditions as of 2001 included age and sex, occupational social class from most recent employment (RGSC), housing tenure (owns outright, buying with mortgage council rented, private rented, other), a binary measure of depressive/anxiety symptoms as indexed by the 12-item GHQ using the standard cut-off of 2/3 points (individual items are listed in the methods chapter), and self-rated health in 2001 (excellent/good/fair/poor). Smoking in 2001 was included (never smoker, ex-smoker, current

(<10/day), current (11-20/day), and current (>20/day), as was categorised BMI using standard WHO classifications (<18.5, 18.5-25.0, 25-30, >30) using height and weight from 2003, since these were not measured in 2001. It was not possible to consider alcohol consumption at or near baseline since no information on this was collected until later waves. In mediation models the following covariates were included from 2011: occupational social class from most recent employment, housing tenure, self-rated health, BMI and dichotomised GHQ score, and 2010: smoking and alcohol consumption (5+ days/week, 3-4 days/week, 1-2 days/week, less often, non-drinker). Current employment status in the month of each participant's nurse visit was also included as covariate, using information from the 2011 and 2012 waves.

5.3.1.3 Multiple imputation

Multiple imputations using chained equations (M=20) were performed on all participants present in 2001 from the initial UK, Scottish and Welsh samples. The imputation models contained outcomes CRP and fibrinogen in log-transformed form, unemployment variables, all covariates from analysis models, information on medications used in sensitivity analyses and a few auxiliary variables (height, weight, and self-rated health in 2006).

The summary variables of unemployment in this analysis were calculated from hundreds of variables corresponding to 110 current and past activity slots between 2001 and UKHLS wave 4 in 2012, and it was not therefore computationally feasible to impute these root variables individually. However, imputing the summary variables themselves would treat inappropriately the 7820 participants present in 2011 who had gaps in their employment history information (in 92.1% of cases due to dropout prior to 2011; the remainder had skipped waves before re-entering). For a person who dropped out after 8 years but had 16 months of reported unemployment prior to dropout, the simple addition of unemployment spells would give a value for the summary variable identical to a person who was present continuously and reported 16 months of unemployment across a 10-year period. This would be incorrect, since it ignores the fifth of their employment history of unknown

composition. On the other hand, treating the summary variable as a missing value would fail to use the partial information, and possibly lead to imputed values which we know to be incorrect (e.g., an imputed total unemployment across 10 years of less than 16 months, which we know is not true from even the partial information).

The solution was to calculate self-contained, annual unemployment durations using reports of current and past activities at each individual wave (this was only possible because of the way I had set up the activity histories, and had not been an option with analyses using the 1958 cohort, for which I used a modified form of an existing dataset structured in a way that precluded this). For the 2.3% of participants who skipped waves but later re-entered, it was possible to use later reports to fill in employment history gaps retrospectively. This resulted in ten variables of unemployment duration corresponding to each wave which were included in imputation models so that partial employment history information could be utilised and remaining gaps filled in the most valid way. For this reason, it was not possible to simultaneously consider number of unemployment spells in addition to total unemployment duration. Firstly, the inclusion of both would have led to substantial collinearity in the imputation models, and secondly, the number of spells could not have been imputed using a strategy of independent annual employment history periods since many spells would continue across several of these periods. The summary variables of total months of unemployment and recentness of last unemployment were calculated post-imputation as passive variables.

5.3.1.4 Analysis

Linear regressions using imputed data were used to examine the impact of past unemployment on log-transformed CRP and fibrinogen, and logistic regression using imputed data were used to examine the impact of past unemployment on odds of CRP>3mg/L. Interactions by gender, country and age group were considered prior to multiple imputation.

Crude models adjusted for age and sex only, and an 'initial conditions' model additionally adjusted for baseline SEP (RGSC and housing tenure), health status (self-reported health and dichotomized GHQ) and health behaviours (smoking and categorized BMI). Further levels of adjustment explored the addition of SEP, health status, current unemployment/economic status and health behaviours in 2011 as potential mediating pathways.

Using STATA's svyset command, all analyses took account of clustering by primary sampling unit and strata, and longitudinal weights for participants continuously present from 2001 through the 2011 nurse visit were used to take account of non-random attrition across the 10-year period. Since participants not continuously present between 2001 and the nurse wave in 2011 had been assigned longitudinal weights of 0, the 7820 participants with partial employment history information were effectively excluded from analysis models, despite contributing to the imputation process.

5.3.1.5 Sensitivity analyses

Sensitivity analyses investigated the impact of restricting the age range further to participants who had been of working age throughout the entire follow-up period, of excluding participants taking medications which would affect inflammation or fibrinogen specifically (NSAIDs, statins, betablockers, lipid-lowering drugs for cholesterol or fibrinogen, anti-fibrolytics or haemostatics, prescribed aspirin, oral contraceptives or hormone replacement therapy), and of considering the time of day, season, and processing time of blood samples.

Table 5.9: Initial conditions models, participants taking anti-inflammatory medications excluded, NCDS (N=7452)					
		Initial sample, aged 15-64 in 2001 N= 11546		Final sample: aged 15-64 in 2001, continuously present 2001-2011 and excluding CRP>10mg/L N=2754 in m=0 N=2685-2714 in imputed data	
		Unimputed data	Imputed data	Unimputed data	Imputed data
		Mean	Mean	Mean	Mean
C-reactive protein		3.10*	1.99**	3.01	2.04
Fibrinogen		2.83[+]	2.78[++]	2.82	2.79
		(%)	(%)	(%)	(%)
Age at baseline	15-31	32.9	32.9	23.2	23.4
	32-47	36.5	36.4	38.2	38.2
	48-64	30.6	30.6	38.6	38.4
Sex	Male	47.1	47.1	43.9	44.1
	Female	52.9	52.9	56.1	55.9
Country (2001)	England	56.4	56.5	60.4	60.6
	Wales	20.2	20.2	19.5	19.3
	Scotland	23.2	23.3	20.0	20.0
	Missing	0.2	-	0.1	-
SEP at baseline: housing tenure	Owns outright	18.0	18.5	22.6	22.7
	Buying w/ mortgage	54.7	56.3	56.7	57.3
	Council rented	15.6	16.1	13.1	12.9
	Private rented/other	8.7	9.1	7.0	7.1
	Missing	2.9	-	0.6	-
SEP at baseline: occupational social class	Professional	4.4	4.4	5.3	5.4
	Managerial	28.1	29.0	31.5	32.2
	Skilled non-manual	23.3	24.4	24.0	24.7
	Skilled manual	18.1	19.1	16.6	17.1
	Semi-skilled	16.0	17.1	15.0	15.4
	Unskilled	5.4	6.1	4.8	5.1
	Missing	4.7	-	2.9	-
Self-rated health at baseline	Excellent	26.2	26.2	26.1	26.3
	Good	46.7	46.7	47.4	47.6
	Fair	18.8	18.8	19.3	19.1
	Poor	6.7	6.7	5.7	5.6
	Very poor	1.6	1.6	1.5	1.4
	Missing	0.0	-	0.0	-
GHQ at baseline	0-2	68.8	72.9	71.7	72.2
	3+	25.1	27.1	27.4	27.8
	Missing	6.0	-	0.9	-
Smoking at baseline	Never smoker	47.1	49.3	51.1	51.6
	Ex-smoker	20.6	21.8	24.7	24.9
	Current, <= 10/day	10.7	11.2	8.3	8.4
	Current, 11-20/day	13.5	14.1	12.1	11.9
	Current, >20/day	3.4	3.5	3.3	3.2
	Missing	4.7	-	0.5	-
BMI at baseline	18.5-24.9	31.3	42.9	41.4	45.6
	25.0-29.9	24.3	36.1	31.5	35.2
	30.0-34.9	8.7	13.7	11.0	12.4
	>35.0	3.4	4.5	4.8	5.2
	<18.5	1.2	2.7	1.4	1.6
	Missing	31.1	-	10.0	-

Housing tenure: 2011	Owns outright	18.1	30.8	37.6	37.6
	Buying w/ mortgage	23.8	46.2	43.7	44.0
	Council rented	6.6	13.9	11.4	11.2
	Pvt rented/other	4.1	9.1	7.2	7.2
	Missing	47.5	-	0.1	-
Occupational social class: 2011	Professional	2.8	5.1	5.0	5.1
	Managerial	17.7	33.3	34.2	34.7
	Skilled non-manual	11.4	22.3	23.1	23.4
	Skilled manual	9.7	19.8	18.7	19.0
	Semi-skilled	6.7	13.8	12.7	12.9
	Unskilled	2.7	5.7	4.8	5.0
	Missing	49.0	-	1.4	-
Long-term illness: 2011	No	33.5	63.8	61.3	61.8
	Yes	19.0	36.2	38.7	38.2
	Missing	47.5	-	-	-
GHQ: 2011	0-2	33.5	75.9	73.3	76.5
	3+	10.0	24.1	22.2	23.5
	Missing	56.5	-	4.5	-
Smoking: 2011	Never smoker	23.2	41.1	42.9	43.1
	Ex-smoker	20.0	35.5	37.0	37.0
	Current, <= 10/day	5.3	10.0	9.0	9.0
	Current, 11-20/day	5.6	10.9	9.2	9.0
	Current, >20/day	1.2	2.4	1.9	1.9
	Missing	44.8	-	0.0	-
Drinking frequency: 2010	Most days	7.7	16.0	14.4	16.0
	2-3 days/week	7.7	15.9	14.6	16.3
	>1/month , < 1/week	14.8	31.6	28.3	31.4
	<1/month	15.4	33.4	30.4	33.7
	Non-drinker	1.1	3.0	2.1	2.6
	Missing	53.4	-	10.2	-
BMI: 2011	18.5-24.9	8.3	25.9	27.9	28.5
	25.0-29.9	11.2	37.2	38.5	39.2
	30.0-34.9	6.2	23.3	20.5	20.5
	>35.0	3.7	11.9	11.6	11.1
	<18.5	0.2	1.7	0.7	0.7
	Missing	70.5	-	0.8	-
Takes potentially anti-inflammatory medications	Yes	22.3	76.1	75.1	75.5
	No	7.4	23.9	24.9	24.5
	Missing	70.3	-	-	-
Takes oral contraceptives or HRT	No	29.1	96.5	98.1	98.1
	Yes	0.6	3.5	1.9	1.9
	Missing	70.3	-	-	-
*Based on 2319 obs **Based on 1833 obs $^{+}$Based on 2310 obs $^{++}$Based on 1826 obs					

Table 5.10: Current and past unemployment in initial and final samples (UKHLS)					
		Initial sample		Final sample	
		Unimputed data	Imputed data	Unimputed data	Imputed data
Employment status 2011	Employed/self-employed	27.4	64.1	61.1	61.4
	Unemployed	1.5	4.4	2.8	2.8
	Sick/Disabled	1.7	4.5	3.8	3.7
	Economically inactive	18.4	27.0	32.3	32.1
	Missing	51.1	-	61.1	-
Total unemployment, 2001-2011	Never unemployed	40.4	77.2	80.3	80.9
	1-6 months	4.6	10.6	9.4	9.5
	7-12 months	2.2	4.6	3.7	3.8
	13-24 months	1.8	3.8	3.1	3.1
	>24 months	1.4	3.8	2.7	2.7
	Missing	49.7	-	0.7	-
Recentness of last unemployment	Never unemployed	40.4	77.2	80.3	80.9
	Current	1.7	4.4	2.8	2.8
	Since 2006	3.7	8.7	7.7	7.8
	2010-2006	4.5	9.7	8.5	8.5
	Missing	49.7	-	0.7	-

Table 5.11: Current and past unemployment in initial and final samples (UKHLS)
Reference group: participants not unemployed in this period

	Log-transformed CRP				CRP > 3mg/L				Log-transformed Fibrinogen			
		Coeff	CI	P		OR	CI	p	Coeff	Coeff	CI	p
Age, sex, country	Up to 6 months	0.08	-0.11,0.28	0.41	Up to 6 months	1.02	0.63,1.67	0.93	Up to 6 months	0.03	-0.01,0.07	0.14
	6-12 months	0.05	-0.24,0.34	0.74	6-12 months	0.85	0.39,1.88	0.69	6-12 months	0.01	-0.05,0.07	0.73
	13-24 months	0.23	-0.13,0.59	0.21	13-24 months	1.56	0.69,3.54	0.28	13-24 months	0.07	-0.01,0.14	0.08
	> 24 months	0.14	-0.26,0.54	0.50	> 24 months	0.75	0.28,1.96	0.55	> 24 months	0.10	0.02,0.17	0.01
Initial Conditions: sex, age, country, housing tenure, RGSC, self-rated health, GHQ, smoking, BMI in 2001		Coeff	CI	P		OR	CI	p		Coeff	CI	p
	Up to 6 months	0.03	-0.15,0.22	0.71	Up to 6 months	0.92	0.54,1.54	0.74	Up to 6 months	0.02	-0.02,0.05	0.35
	6-12 months	0.05	-0.24,0.35	0.71	6-12 months	0.82	0.34,1.97	0.65	6-12 months	0.00	-0.06,0.07	0.88
	13-24 months	0.09	-0.27,0.45	0.63	13-24 months	1.24	0.49,3.11	0.64	13-24 months	0.04	-0.03,0.11	0.27
	> 24 months	0.01	-0.38,0.39	0.98	> 24 months	0.54	0.20,1.48	0.23	> 24 months	0.08	-0.00,0.15	0.06

Table 5.12: Recentness of unemployment 2001-2011 with inflammatory markers in 2011 (participants currently sick/disabled excluded) (UKHLS)
Reference group: participants not unemployed in this period and not currently sick/disabled

ADJUSTMENT LEVEL	Log-transformed CRP				CRP > 3mg/L				Log-transformed Fibrinogen			
Age, sex, country		Coeff		P		OR	CI	p		Coeff	CI	p
	Current	0.37	-0.04,0.78	0.08	Current	1.92	0.83,4.41	0.12	Current	0.11	0.02,0.19	0.01
	2006-2011	0.00	-0.21,0.22	0.97	2006-2011	0.69	0.38,1.26	0.22	2006-2011	0.03	-0.02,0.07	0.22
	Before 2006	0.13	-0.10,0.36	0.26	Before 2006	1.12	0.63,1.97	0.70	Before 2006	0.03	-0.02,0.07	0.22
Initial Conditions: sex, age, country, housing tenure, RGSC, self-rated health, GHQ, smoking, BMI in 2001		Coeff		P		OR	CI	p		Coeff	CI	p
	Current	0.24	-0.16,0.63	0.23	Current	1.51	0.60,3.82	0.37	Current	0.07	-0.01,0.16	0.09
	2006-2011	-0.04	-0.25,0.17	0.71	2006-2011	0.61	0.32,1.16	0.13	2006-2011	0.01	-0.03,0.06	0.56
	Before 2006	0.06	-0.15,0.27	0.56	Before 2006	0.94	0.51,1.74	0.84	Before 2006	0.02	-0.03,0.06	0.48

5.3.2 Results

The initial and final samples (Tables 5.9, table 5.10) differed with respect to most characteristics. A comparison of participants excluded and participants retained in analytic models using imputed data showed that retained participants were significantly older, more likely to be female, and from England. They smoked less and had lower BMI at both time-points. They were more likely to be homeowners at both time-points, and of more advantaged occupational social class at baseline. They had less past unemployment and were less likely to be currently unemployed than excluded participants (all $p<0.05$).

5.3.2.1 Total unemployment in months, 2001-2011

In crude models adjusting only for age sex and country (Table 5.11), only log-transformed fibrinogen was significantly associated with total unemployment over the study period, and only for the top group of >24 months when compared to participants never unemployed (coeff: 0.10,p=0.01) with a suggestion of a smaller effect for the 13-24 months group (coeff: 0.07, p=0.08). However, both associations reduced substantially with adjustment for initial conditions, to coeff: 0.08, p=0.06 and 0.04, p=0.27) respectively. Successive models showed that any remaining effects were explained more by current unemployment in 2011 than other factors (Table 5.13). Suppression of CRP effects by health behaviours was checked for, but not supported for the log-transformed or binary outcome.

5.3.2.2 Most recent unemployment, 2011

In models adjusted for age, sex and country (Table 5.12), participants last unemployed in 2006-2011 or 2001-2006 did not have significant elevations for any biomarker, and only log-transformed fibrinogen was significantly elevated for currently unemployed participants (coeff: 0.11, p=0.01). Adjustment for initial conditions reduced this to 0.08, p=0.09. Successive models (Table 5.13) indicated that current SEP, physical and mental health and health behaviours do not explain this

effect. Suppression of CRP effects by health behaviours in this population was not supported, since effect sizes for both CRP outcomes reduced with additional adjustment for smoking, drinking and BMI in 2011.

Table 5.13: Further adjustment for fibrinogen analyses (UKHLS)				
Total Unemployment 2001-2011				
SEP pathway: Initial conditions + SEP in 2011		Coeff	CI	P
	Up to 6 months	0.02	-0.02,0.05	0.39
	6-12 months	0.00	-0.06,0.06	0.97
	13-24 months	0.04	-0.04,0.11	0.33
	> 24 months	0.07	-0.01,0.15	0.07
Health pathway: Initial conditions + physical health + GHQ in 2011		Coeff	CI	P
	Up to 6 months	0.02	-0.02,0.05	0.34
	6-12 months	0.00	-0.06,0.06	0.89
	13-24 months	0.04	-0.03,0.11	0.27
	> 24 months	0.07	-0.01,0.15	0.07
Current unemployment pathway: Initial conditions + current unemployment in 2011		Coeff	CI	p
	Up to 6 months	0.01	-0.02,0.05	0.43
	6-12 months	0.00	-0.06,0.06	0.98
	13-24 months	0.03	-0.04,0.10	0.36
	> 24 months	0.05	-0.03,0.14	0.22
Health behaviours pathway: Initial conditions + health behav's in 2011		Coeff	CI	p
	Up to 6 months	0.02	-0.02,0.06	0.29
	6-12 months	0.00	-0.06,0.06	0.98
	13-24 months	0.04	-0.03,0.11	0.22
	> 24 months	0.07	-0.01,0.15	0.10
		Coeff	CI	p
Full adjustment: all factors above	Up to 6 months	0.02	-0.02,0.05	0.37
	6-12 months	-0.01	-0.07,0.05	0.78
	13-24 months	0.04	-0.03,0.10	0.30
	> 24 months	0.05	-0.04,0.14	0.28
Recentness of unemployment 2001-2011				
SEP pathway: Initial conditions + SEP in 2011		Coeff	CI	p
	Current	0.07	-0.02,0.16	0.11
	2006-2011	0.01	-0.03,0.05	0.63
	Before 2006	0.01	-0.03,0.06	0.52
Health pathway: Initial conditions + physical health + GHQ in 2011		Coeff	CI	p
	Current	0.07	-0.01,0.16	0.08
	2006-2011	0.01	-0.03,0.06	0.56
	Before 2006	0.02	-0.03,0.06	0.47
Health behaviours pathway: Initial conditions + health behav's in 2011		Coeff	CI	p
	Current	0.07	-0.02,0.15	0.12
	2006-2011	0.01	-0.03,0.06	0.51
	Before 2006	0.01	-0.03,0.06	0.48
Full adjustment: all factors above		Coeff	CI	p
	Current	0.06	-0.02,0.14	0.13
	2006-2011	0.01	-0.03,0.05	0.57
	Before 2006	0.01	-0.03,0.06	0.49

5.3.2.3 Results of sensitivity analyses

Exclusion of participants taking medications expected to affect CRP or fibrinogen did not alter conclusions (Table 5.14). Effect sizes for associations of current unemployment and CRP outcomes appeared to increase, but the substantial drop in sample size (24% of the final sample were taking

such medication) in an already underpowered sample means the influence of such medication cannot be compared fairly.

Table 5.14: Initial conditions models, participants taking potentially anti-inflammatory medications excluded (UKHLS)									
	Log-transformed CRP			Odds of CRP>3mg/L			Log-transformed Fibrinogen		
TOTAL UNEMPLOYMENT (N=2034)	Coeff	CI	P	OR	CI	P	Coeff	CI	p
Up to 6 months	0.06	-0.15,0.27	0.55	0.98	0.53,1.79	0.94	0.02	-0.02,0.06	0.31
6-12 months	0.09	-0.23,0.41	0.57	0.89	0.34,2.31	0.80	0.01	-0.06,0.08	0.74
13-24 months	0.19	-0.21,0.59	0.34	1.58	0.58,4.33	0.37	0.04	-0.05,0.13	0.37
> 24 months	-0.01	-0.41,0.40	0.97	0.55	0.19,1.60	0.27	0.07	-0.01,0.15	0.08
RECENTNESS OF LAST UNEMPLOYMENT	Coeff	CI	P	OR	CI	P	Coeff	CI	p
Current	0.30	-0.14,0.75	0.18	1.77	0.66,4.75	0.25	0.07	-0.02,0.16	0.11
2006-2011	-0.01	-0.24,0.22	0.95	0.69	0.34,1.37	0.28	0.02	-0.03,0.06	0.51
Before 2006	0.11	-0.13,0.35	0.36	1.05	0.51,2.17	0.89	0.02	-0.03,0.07	0.44

Conclusions did not change with models restricted to participants of working age throughout the entire study period, although again the drop in precision resulting from further restriction of the sample made a direct comparison impossible. Neither did conclusions change with inclusion of the season and time of day (morning/afternoon/evening) of the nurse visit and the processing time (less than 1 day, 1 day, 2 days, 3 or more days) of the sample.

5.4 Discussion

5.4.1 1958 Cohort Study

After adjustment for SEP, mental and physical health at labour market entry, a roughly stepwise association was observed between total aggregated unemployment and fibrinogen, but not CRP. As with analyses in this dataset of the inflammation-depression association, this casts doubt on the existence of an overall relationship with systemic inflammation, but is consistent with an independent impact of aggregated unemployment on fibrinogen specifically via an alternative

pathway. Since mediation models showed the association with fibrinogen was largely explained by SEP, such a pathway would likely be indirect.

In contrast to total aggregated unemployment, no association was visible between number of unemployment spells and fibrinogen. This could reflect differential inaccuracies in the data: if recall error affects reporting of short events more than longer ones, we would expect the accuracy of the number of spells to be less than that of total aggregated unemployment, since the latter would often be determined by a few periods of long duration. Since random misclassification of exposure always leads to underestimation of effects, this could explain the observed discrepancy. Alternatively, it is possible that fibrinogen is genuinely more affected – directly or otherwise – by unemployment duration than the transition from employment to unemployment.

Meanwhile, the lack of associations of either marker with discrete unemployment spells ending within the past 5 years or before suggests any effects of discrete spells, working via inflammation or additional pathways affecting fibrinogen, are largely transitory. That associations of current unemployment and three measures of systemic inflammation at age 45 presented in chapter 4 proved robust to further adjustment for 'initial conditions' at labour market entry provides further support for a cross-sectional relationship independent of confounders.

5.4.1.1 Limitations

This analysis had several limitations. The first concerns the quality of the data. While the updated version of the AHD provides a more accurate account of participants' activity histories in the years prior to outcome measurement, the process of reconciling discrepant accounts was a sobering reminder of the inaccuracy of retrospectively given accounts. Since elsewhere in participants' activity histories there are even longer periods described only by retrospective accounts, for instance a 10-year period between age 23 and age 33, these periods will likely contain substantial errors leading to misclassification of exposure.

Secondly, exclusion of participants was non-random in a way which may have led to underestimation of effects. Participants excluded because they did not have activity history records were, at labour market entry, of more disadvantaged SEP and with greater internalising and externalising symptoms. Given that experience of unemployment is predicted by SEP at labour market entry, and inflammation at 45 appears in this population to be predicted by externalising and externalising symptoms, these exclusions may have produced underestimation of effects to the extent that the tails of both outcome and exposure will be missing.

Finally, the fact that all participants in the sample are the same age means it was impossible to separate recentness of unemployment from the age at which it occurred.

5.4.2 UKHLS

As with the 1958 Cohort, models of aggregated unemployment found no evidence for an association of past unemployment with CRP, but some evidence for associations with fibrinogen. This again suggests that unemployment and fibrinogen may be linked via a non-inflammatory pathway. This is consistent with the pattern of medication use in this population, since only one person in the final sample reported a prescription of anti-fibrolytics or haemostatics but 1032 people reported use of NSAIDs or other medications expected to affect inflammation. While associations with fibrinogen did not reach significance, effect sizes were considerably larger than in NCDS analyses, consistent with this being an underpowered data source. In contrast to NCDS analyses, in UKHLS the association with fibrinogen was better explained by current unemployment at outcome measurement than SEP or health behaviours. This may reflect the different timescales over which aggregated unemployment was considered in the NCDS and UKHLS data (29 years and 10 years respectively) since past unemployment might be expected to correlate more strongly with current unemployment on a shorter timescale, but have more impact on SEP and/or health behaviours over a longer one.

Recentness analyses accord with results of cross-sectional analyses using the larger UKHLS population from which this BHPS subsample was drawn, since no such cross-sectional associations with CRP were found there even for current unemployment (i.e., maximum recentness).

5.4.2.1 Limitations

The annual collection of data in this survey should have reduced recall error and hence misclassification of exposure, while use of longitudinal weights should have minimised impact of non-random attrition over the 10-year period. Nevertheless, a major limitation of this dataset concerns the small number of participants continuously present over the 10-year period and also present at the nurse wave, with the result that analyses were underpowered. Moreover, it is likely that the UKHLS sample was further impacted by non-random exclusion from final models. Participants who had experienced much unemployment were substantially under-represented in the final analytic sample, despite use of imputation to minimise loss. Participants from Scotland and Wales were under-represented compared to participants from England, which may have biased associations downwards if, judging by results of chapter 4, we would expect stronger associations where unemployment had been higher in this historical period.

5.4.3 Support for hypotheses

Contrary to the stated hypotheses, these analyses did not support an overall association of total aggregated unemployment or number of spells with markers of systemic inflammation. No evidence was found for an association with recent but non-current spells, or for a sensitive period effect of unemployment soon after labour market entry.

5.4.4 Fit with previous research

Only one study had been published of longitudinal associations between unemployment and inflammation[119]. Janicki-Deverts reported that in a population of 1,117 young men from the US-based CARDIA study, CRP was elevated at year 15 of follow-up for participants who had experienced

an unemployment spell of 2 months or longer between year 7 and year 10, i.e. 5-8 years previously. This was robust to adjustment for age, race, year 7 CRP, year 15 BMI, average income across years 10 and 15, and current or recent unemployment at year 15. Given this previous finding, the lack of an association with recent but ended unemployment in both NCDS and UKHLS data was unexpected.

Since the CARDIA study contains only men, one obvious explanation for the difference would be that, as hypothesised in the context of unemployment's effects on mental health, associations with CRP are stronger for men. However, interactions with gender had been tested for prior to imputation in both datasets for all past unemployment variables, and none found. Furthermore, when gender-stratified models were run in both imputed and unimputed data, robust effects did not emerge for the male component of either study population.

Methodological differences between the studies may also have affected results. In the CARDIA study adjustment was made for age, ethnicity, BMI at outcome, average income in the 5 years before outcome, current or recent unemployment at outcome, and baseline CRP. While adjustment for baseline CRP is clearly an advantage compared to the NCDS and UKHLS analyses, there is no adjustment for pre-existing long-term illness, or socioeconomic or psychological 'initial conditions' which may have affected both unemployment and later CRP and thus confounded the relationship.

Another possible explanation concerns welfare differences in the two countries. Since an established literature exists showing that cross-sectional associations of unemployment and poor health tend to be stronger in countries with less generous unemployment protection[127], it should perhaps not be surprising that longitudinal associations of unemployment and inflammation appeared stronger in a US population than a UK one. It has for example been suggested that in countries with less generous unemployment protection jobseekers will be forced to accept lower-quality or lower-waged work sooner, decreasing the duration of the average unemployment spell but increasing its long-term economic impact[281]. While Janicki-Deverts' study did adjust for average income in the five years prior to income, it should be noted that the reduction in scarring effects associated with more

generous unemployment protection appears to extend to non-financial aspects of subsequent job quality including length of contract [282, 283]. Insofar as they are mediated by quality of subsequent work, we might expect long-term health impacts of unemployment to vary accordingly. Lastly, since no information was provided on medication use in that population, it is possible that use of anti-inflammatory medications in the CARDIA sample was lower, allowing inflammatory effects of social exposures to be detected.

5.5 Chapter Summary

Despite cross-sectional associations of unemployment and markers of systemic inflammation presented in Chapter 4, longitudinal analyses using the NCDS and UKHLS do not support the existence of scarring effects of past unemployment on systemic inflammation. However, an apparent association of past unemployment and fibrinogen suggests an alternative pathway may be operating involving that biomarker specifically, mediated by SEP, later unemployment and/or health behaviours. Taken together with the robust cross-sectional association observed across the various UK samples of CRP, fibrinogen and current unemployment, this suggests that any inflammatory effects of unemployment are not long-lasting after employment has been regained.

In the next chapter, results are presented of prospective analyses investigating the association of markers of systemic inflammation with later depressive symptoms. Given the evidence presented in chapter 4 for an association of current unemployment and systemic inflammation, a predictive association of systemic inflammation with later depressive symptoms could still suggest that inflammation may mediate between unemployment and depressive symptoms, warranting further investigation of the impact of unemployment on depressive symptoms in these terms.

6 INFLAMMATION-DEPRESSION DIRECTIONALITY

6.1 Chapter Overview

This chapter presents results of analyses relating to objective 3: to investigate the directionality of associations between inflammation and depressive symptoms. Firstly, methods and results are presented and discussed for NCDS, and in the following section methods and results are presented and discussed for UKHLS. The final section of this chapter discusses results of both sets of analyses in relation to each other, hypotheses relating to objective 3, and previous literature on this topic.

It was hypothesised that baseline inflammatory markers would be positively associated with later depressive symptoms after controlling for depressive symptoms at baseline, supporting the cytokine theory of depression, and a mediating role for systemic inflammation in associations between unemployment and depressive symptoms.

6.2 Analyses Using 1958 Cohort Study

6.2.1 Methods

6.2.1.1 Participants

Because of substantial missingness for both inflammatory markers and covariates, multiple imputation by chained equations was used to deal with missingness in the data. Imputation models were run on all participants in the NCDS (N=18558). Analysis models were restricted to participants who were present at sweep 6, the biomedical sweep and sweep 8 (when baseline MI score, inflammatory markers and outcome MI score, were respectively measured), were not pregnant at any of these sweeps and did not have CRP>10mg/L. This left a final sample size which varied between 9042 and 9067 across 20 imputations.

6.2.1.2 Measures

6.2.1.2.1 Inflammatory markers

Systemic inflammation was indexed by C-reactive protein and fibrinogen. As with other analyses, both CRP and fibrinogen were log-transformed prior to analysis and CRP was also studied as a dichotomous outcome using the standard cut-point of 3mg/L. Participants with CRP>10mg/L were excluded from both CRP and fibrinogen analyses post-imputation to isolate systemic inflammation from acute inflammation associated with current infection.

6.2.1.2.2 Depressive symptoms

At the biomedical sweep of NCDS when inflammatory markers were measured, depressive symptoms were measured using the CIS-R, in contrast to the Malaise Inventory used at every other adulthood sweep. The result of this inconsistency is that depressive symptoms 'at baseline' – when exposure was measured - are not directly comparable with later depressive symptoms, the outcome in this analysis. This analysis therefore investigated whether depressive symptoms at sweep 8 (the first measurement following the biomedical sweep, 5-6 years later) were predicted by markers of systemic inflammation at the biomedical sweep, adjusted for depressive symptoms at sweep 6. This meant the two measures of depressive symptoms – both Malaise Inventory – were directly comparable. However, since sweep 6 was approximately 2 years before measurement of inflammation, sweep 6 MI score should be regarded as a proxy for depressive symptoms at baseline rather than a direct measurement.

Depressive symptoms at age 50 were measured using the 9-item Malaise Inventory, as both a continuous measure and a binary outcome using the standard cut-off of 4+. Since the full 24-item version of the questionnaire was used at age 42, but the shorter 9-item version at age 50, the 9 questions asked at both sweeps were drawn out from the age 42 data and summary measures calculated using these items.

6.2.1.2.3 Covariates

Gender and SEP (RGSC from current or most recent employment, housing tenure) at 42 were assessed by questionnaire. Since both depression and inflammation in middle age may be independently affected by early life factors, parental social class at birth was also included to guard against confounding by childhood circumstances.

Presence at age 42 of somatic illnesses characterised by inflammation which could also plausibly predict depression were adjusted for. This included diabetes and cancer, respiratory infections (asthma and bronchitis), Crohn's disease, and Inflammatory Bowel Disorder.

The impact was also explored of health behaviours at 42, all self-reported by questionnaire. Smoking was classified as never smoker, ex-smoker, current smoker (up to 10/day), current (10-20/day), and current (21+/day). Alcohol consumption was indexed by frequency of drinking occasions: on most days, 2-3 days/week, once a week, less often, and non-drinker. Adiposity was indexed using WHO BMI categories (<18.5, 18.5-24.99, 25-29.99, 30-34.99, ≥35), calculated from self-reported height and weight. Implausible outlying values of height and weight were recoded to missing (by inspecting the top and bottom 2.5% of height and weight distribution) and imputed back.

6.2.1.3 Analysis

Linear regression was used to look at CRP and fibrinogen in relation to MI at 50 as a continuous outcome, and logistic regressions used to look at CRP and fibrinogen at 45 in relation to Malaise Inventory at age 50 (whether a participant scored at or above the standard cut-off of 4 points).

6.2.1.3.1 Sensitivity analyses

Sensitivity analyses explored the impact of excluding several groups: participants taking potentially anti-inflammatory medications (NSAIDs, statins, systemic corticosteroids, and fibrates for fibrinogen analyses) participants taking antidepressants, participants taking oral contraceptives or receiving hormone replacement therapy, and participants who were peri-menopausal during this time

(defined as still having periods at 45 but not at age 50, and attributing this to the menopause). The impact of the time of day, season, and processing time of blood samples was also considered.

6.2.2 Results

6.2.2.1 Comparison of initial and final samples

Table 6.1 shows unimputed and imputed data for initial and final samples. A comparison using imputed data showed that compared to participants excluded, participants retained in final models were more likely to be female, of more advantaged SEP at birth and age 42, and less likely to have relevant somatic illness at baseline or above-cutoff depressive symptoms at either time-point. They drank more, smoked less, typically had lower BMI, and were less likely to be taking anti-inflammatory medications or antidepressants (all $p<0.05$). They were not more likely to be taking HRT or be peri-menopausal. Due to the exclusion of participants with CRP>10mg/L, mean levels of both inflammatory markers were lower in the final sample compared to the initial sample.

6.2.2.2 Associations with CRP

Initial associations in sex-adjusted models of CRP at 45 with Malaise Inventory at 50 were robust to adjustment for MI at 42 although effect sizes did attenuate slightly (Table 6.2). Additional adjustment for SEP at birth and age 42 and relevant somatic illnesses at 42 attenuated associations further, suggesting these factors may partially confound associations of inflammation and depressive symptoms around this age. Any remaining associations were explained by addition of health behaviours (smoking and drinking at 42, BMI at 45) at which point associations with both log-transformed MI score and odds of above-cutoff score approached the null.

Table 6.1: Characteristics of initial and final samples (NCDS)

		Initial sample: all NCDS N=18,558		Final sample: present at sweep 6, biomedical and sweep 8, pregnant at none, and with CRP<=10mg/L N=7746 in m=0 N=9042-9067 in imputed data	
		Unimputed	Imputed data	Unimputed	Imputed
BASELINE CHARACTERISTICS		(%)	(%)	(%)	(%)
Sex	Male	51.7	51.7	49.0	49.1
	Female	48.3	48.3	51.0	50.9
	Missing	0.0	-	-	-
Inflammatory markers		Mean	Mean	Mean	Mean
	C-reactive protein (mg/L)	2.18 *	2.40	1.62**	1.62
	Fibrinogen (g/L)	2.96[+]	2.99	2.91[++]	2.91
		(%)	(%)	(%)	(%)
Social class at birth	Professional	4.0	4.4	4.7	5.1
	Managerial	11.5	12.3	13.5	14.4
	Skilled non-manual	8.6	9.1	9.4	9.9
	Skilled manual	45.1	47.9	45.3	47.6
	Semi-skilled	10.8	11.4	10.7	11.2
	Unskilled	8.7	9.3	7.0	7.4
	No male head/Forces	5.2	5.6	4.3	4.5
	Missing	6.2	-	5.2	-
SEP: housing tenure	Owns outright	5.1	8.2	8.3	8.4
	Buying w/ mortgage	44.2	71.0	76.2	76.6
	Council rented	7.3	7.7	8.9	6.2
	Private rented/other	4.5	13.1	6.2	8.8
	Missing	38.9	-	0.4	-
SEP: occupational social class at 42	Professional	2.9	4.9	5.7	5.7
	Managerial	19.7	33.8	37.0	37.3
	Skilled non-manual	12.2	21.8	21.8	22.1
	Skilled manual	11.1	20.2	18.6	18.8
	Semi-skilled	7.7	14.8	12.5	12.8
	Unskilled	2.2	4.6	3.1	3.2
	Missing	44.2	-	1.4	-
Relevant somatic illness	Yes	10.6	17.4	16.7	16.6
	No	51.0	82.6	83.3	83.4
	Missing	38.5	-	0.0	-
MI at sweep 6	0-3	52.8	86.1	87.4	88.0
	4+	7.9	13.9	12.0	12.0
	Missing	39.3	-	0.6	-
Smoking	Never smoker	27.3	44.2	46.7	46.8
	Ex-smoker	15.5	24.5	26.0	26.1
	Current, <= 10/day	7.0	11.4	11.0	11.0
	Current, 11-20/day	8.7	14.9	12.6	12.5
	Current, >20/day	2.8	5.0	3.5	3.5
	Missing	38.7	-	0.1	-
Drinking frequency	Most days	12.1	19.7	20.2	20.2
	2-3 days/week	19.8	32.0	33.3	33.4
	1 day/week	18.0	29.3	29.8	29.8
	Less often	8.1	13.4	12.2	12.1
	Non-drinker	3.3	5.6	4.5	4.5
	Missing	38.7	-	0.1	-

BMI	18.5-24.9	16.8	31.1	33.7	34.4
	25.0-29.9	20.5	39.6	40.7	41.2
	30-34.9	8.4	19.6	16.6	16.9
	>35	3.7	8.2	6.8	7.0
	<18.5	0.3	1.5	0.5	0.5
	Missing	50.4	-	1.7	-
Takes potentially anti-inflammatory medications	No	45.2	88.7	90.2	90.3
	Yes	5.3	11.3	9.8	9.7
	Missing	49.5	-	0.0	
Takes Antidepressants	No	47.6	93.5	94.8	94.8
	Yes	2.9	6.5	5.2	5.2
	Missing	49.5	-	0.0	-
HRT or oral contraceptives use	No	72.6	91.1	91.2	91.3
	Yes	4.5	8.9	8.8	8.7
	Missing	22.9	-	0.0	-
Menopause 44-50	No	69.4	89.1	89.2	89.2
	Yes	4.8	10.9	10.8	10.8
	Missing	25.8	-	0.0	-
OUTCOME CHARACTERISTICS					
MI at sweep 8	0-3	44.2	84.2	85.6	86.3
	4+	7.6	15.8	13.6	13.7
	Missing	48.2	-	0.9	-
*Based on 7692 obs **Based on 6369 obs $^{+}$Based on 7683 obs $^{++}$Based on 6362 obs					

6.2.2.3 Associations with Fibrinogen

Associations with fibrinogen were noticeably stronger than associations with CRP (Table 6.2). While addition of MI at 42, SEP, relevant somatic illnesses, and health behaviours to the model did produce attenuation substantial effects sizes remained after full adjustment, significantly so for odds of above-cutoff MI.

Table 6.2: Association of inflammatory markers at 45 with Malaise Inventory at 50						
CRP (log-transformed)	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	p
Crude: Age and sex	0.08	0.04-0.12	<0.001	1.13	1.06-1.21	<0.001
Base model: Age, sex, MI at 42	0.05	0.01-0.08	0.006	1.13	1.05-1.21	0.002
Base model + SEP at birth	0.04	0.01-0.08	0.02	1.12	1.04-1.20	0.004
Base model + SEP at birth and 42	0.03	-0.01-0.07	0.09	1.09	1.01-1.17	0.03
Base model + SEP at birth and 42, somatic illness at 42	0.03	-0.01-0.06	0.16	1.08	1.00-1.16	0.05
Full: Base model + SEP at birth and 42, somatic illness and, health behaviours	0.01	-0.03-0.05	0.72	1.04	0.95-1.13	0.42
Fibrinogen (log-transformed)	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	p
Crude: Age and sex	0.57	0.33-0.80	<0.001	2.59	1.76-3.83	<0.001
Base model: Age, sex, MI at 42	0.42	0.22-0.62	<0.001	2.59	1.68-3.99	<0.001
Base model + SEP at birth	0.39	0.19-0.59	<0.001	2.49	1.61-3.85	<0.001
Base model + SEP at birth and 42	0.31	0.11-0.51	0.003	2.09	1.35-3.25	<0.001
Base model + SEP at birth and 42, somatic illness at 42	0.30	0.10-0.50	0.004	2.05	1.32-3.19	<0.001
Full: Base model + SEP at birth and 42, somatic illness, and health behaviours	0.21	-0.00-0.42	0.05	1.76	1.10-2.82	0.02

To further unpick the role of health behaviours, additional analysis (Table 6.3) were carried out in which smoking, drinking, and BMI were added one by one and as a group to the base model, and effects compared to the addition to the base model of i) SEP at birth and 42 and ii) relevant somatic illnesses. This confirmed the importance of health behaviours which, as a group, produced the most attenuation. Individual effects were overall strongest for BMI and weakest for alcohol consumption.

Table 6.3: Attenuation of effects with adjustment for individual covariates (NCDS)						
Association of Inflammatory markers at 45 with Malaise Inventory at 50						
CRP (log-transformed)	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	P
Base model: Sex, MI at 42	0.05	0.01-0.08	0.006	1.13	1.05-1.21	0.002
Base model + smoking	0.04	0.00-0.07	0.04	1.11	1.03-1.19	0.008
Base model + drinking	0.04	0.01-0.08	0.02	1.12	1.04-1.21	0.004
Base model + BMI	0.04	-0.00-0.07	0.07	1.09	1.01-1.18	0.05
Base + all health behaviours	0.02	-0.02-0.06	0.37	1.06	0.97-1.15	0.20
Base model + SEP	0.03	-0.01-0.07	0.09	1.09	1.01-1.17	0.03
Base model + somatic illness	0.04	0.01-0.08	0.01	1.12	1.04-1.20	0.004
Fibrinogen (log-transformed)	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	P
Base model: Sex, MI at 42	0.42	0.22-0.62	<0.001	2.59	1.68-3.99	<0.001
Base model + smoking	0.34	0.13-0.54	0.001	2.28	1.47-3.54	<0.001
Base model + drinking	0.38	0.18-0.58	<0.001	2.48	1.60-3.86	<0.001
Base model + BMI	0.37	0.17-0.57	<0.001	2.27	1.45-3.57	<0.001
Base + all health behaviours	0.25	0.03-0.46	0.02	1.90	1.19-3.03	0.007
Base model + SEP	0.31	0.11-0.51	0.003	2.09	1.35-3.25	0.001
Base model + somatic illness	0.41	0.21-0.61	<0.001	2.53	1.64-3.91	<0.001

One possible explanation of the observed attenuation with health behaviours at baseline was that recent changes to smoking, drinking, or BMI shortly before baseline had impacted inflammation which would in turn affect depressive symptoms at outcome (i.e., with inflammation mediating the impact of changes to health behaviours on later depressive symptoms). To test this, models were re-run adding to the base model i) BMI at sweep 6 (rather than the biomedical sweep) and ii) smoking, drinking, and BMI from sweep 5/age 33 (Table 6.4). However, the influence of earlier health behaviours was almost identical, against this explanation.

Table 6.4: Substitution of earlier health behaviours (NCDS)						
Association of Inflammatory markers at 45 with Malaise Inventory at 50						
CRP (log-transformed)	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	p
Base + most recent health behaviours	0.02	-0.02-0.06	0.37	1.06	0.97-1.15	0.20
Base + smoking, drinking and BMI from sweep 6	0.01	-0.02-0.05	0.50	1.05	0.97-1.14	0.26
Base + smoking, drinking and BMI from sweep 5	0.02	-0.02-0.06	0.25	1.07	0.99-1.16	0.09
Association of age 45 Fibrinogen (log-transformed) with Malaise Inventory at 50						
	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	p
Base + most recent health behaviours	0.25	0.03-0.46	0.02	1.90	1.19-3.03	0.007
Base + smoking, drinking and BMI from sweep 6	0.22	0.02-0.43	0.04	1.82	0.15-2.89	0.01
Base + smoking, drinking and BMI from sweep 5	0.26	0.06-0.47	0.01	1.98	1.25-3.13	0.004

Next, I investigated the impact of substituting a different baseline MI measure – namely, the average of the two MI from sweeps 6 and 5 (age 33 and age 42) – rather than simply using the closest MI measurement to the biomedical sweep (that from sweep 6). This was to see whether there was any evidence that, as a result of substantial lability or measurement error due to short-term variation in any particular measure of Malaise Inventory, adjustment for a single measurement of MI at 42 was not adjusting for typical depressive symptoms around baseline as effectively as had been hoped. In Table 6.5, the results are shown of models a) adjusted only for sex and the new measure of previous MI, and b) full adjusted, using the new measure of previous MI. Interestingly, this found that adjusting for the average of MI at 33 and 42 had more of an attenuating effect than adjusting for MI at 42. This suggested that, even though the single measure was an index of more recent depressive symptoms at the time of biomedical sweep, it may have been a less good measure of typical depressive symptoms around the time when the inflammatory markers were measured.

Table 6.5: Substitution of averaged MI score at age 33/42(NCDS)						
Association of Inflammatory markers at 45 with Malaise Inventory at 50						
CRP (log-transformed)	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	P
Base: Sex +MI at 33/42	0.03	-0.00-0.07	0.08	1.12	1.04-1.20	0.002
Full	-0.00	-0.04=0.04	0.94	1.03	0.95-1.12	0.52
Association of age 45 Fibrinogen (log-transformed) with Malaise Inventory at 50						
	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	P
Base: Sex +MI at 33/42	0.32	0.12-0.51	0.001	2.43	1.59-3.72	<0.001
Full	0.17	-0.04-0.38	0.11	1.64	1.03-2.61	0.04

6.2.2.4 Sensitivity analyses

The exclusion of participants taking anti-inflammatory medications, antidepressants, HRT, or oral contraceptives from fully-adjusted models did not affect conclusions for either CRP or fibrinogen. Exclusion of peri-menopausal women and taking into account the time of day, season, and processing time of blood samples also did not substantially affect results (Table 6.6).

Table 6.6: Sensitivity analyses: association of inflammatory markers at 45 with Malaise Inventory at 50 (NCDS)						
CRP (log-transformed) *All estimates are fully-adjusted*	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	P
Excluding participants taking anti-inflammatory meds, HRT, or OCs	0.01	-0.03,0.06	0.51	1.05	0.95,1.15	0.32
Excluding participants taking antidepressants	0.00	-0.04,0.04	0.86	1.02	0.93,1.12	0.65
Excluding peri-menopausal women	0.01	-0.03,0.05	0.73	1.02	0.94,1.12	0.62
Adjusting for season, time of day, and processing time	0.01	-0.03,0.05	0.63	1.05	0.96,1.14	0.31
Fibrinogen (log-transformed) *All estimates are fully-adjusted*	Linear model: Malaise Inventory at 50			Logistic Model: Malaise Inventory (4+) at 50		
	Coeff	CI	P	OR	CI	P
Excluding participants taking anti-inflammatory meds, HRT, or OCs	0.25	0.03,0.48	0.03	1.81	1.07,3.07	0.03
Excluding participants taking antidepressants	0.17	-0.04,0.38	0.12	1.70	1.04,2.79	0.03
Excluding peri-menopausal women	0.20	-0.01,0.41	0.07	1.77	1.08,2.91	0.02
Adjusting for season, time of day, and processing time	0.22	0.01,0.43	0.04	1.87	1.18,2.96	0.01

6.3 Analyses Using Understanding Society

6.3.1 Methods

6.3.1.1 Analytic sample

This analysis began with all participants present at the nurse visit (N=20,685), which took place during W2 for new UKHLS participants and W3 for the BHPS component of the sample. Restriction of analysis models to participants who were also present one year later (W3 for new UKHLS participants and W4 for the BHPS component of the sample), did not have CRP>10mg/L at baseline, and were assigned non-zero values of the appropriate longitudinal weight (1519 participants were excluded on this basis) resulted in a final sample size of 15819 before imputation and 15404-15473 in the imputed data. The entire age range of 16-102 at baseline was used.

6.3.1.2 Measures

6.3.1.2.1 Inflammatory markers

Systemic inflammation was indexed by C-reactive protein and fibrinogen. As with other analyses, both CRP and fibrinogen were log-transformed prior to analysis and CRP was also studied as a dichotomous outcome using the standard cut-point of 3mg/L. Participants with CRP>10mg/L were excluded from both CRP and fibrinogen analyses post-imputation to isolate systemic inflammation from acute inflammation associated with current infection.

6.3.1.2.2 Depressive symptoms

Depressive symptoms were in this analysis measured by the 12-item General Health Questionnaire (GHQ) at both baseline and outcome. This was considered as both a continuous outcome and as a binary measure using the standard cut-off of 3. Both sets of models adjusted for the equivalent measure at baseline.

6.3.1.2.3 Covariates

Models adjusted for age, gender, and two dimensions of SEP at baseline: occupational social class from most recent employment (RGSC), housing tenure (owns outright, buying with mortgage council rented, council/LHA/Housing association rented or private rented/other). BMI was calculated from height and weight measured at the nurse visit, using standard WHO classifications (<18.5, 18.5-25.0, 25-30, 30-35, >35). Smoking (never smoker, ex-smoker, current (<10/day), current (11-20/day), and current (>20/day)) and alcohol consumption (5+ days/week, 3-4 days/week, 1-2 days/week, less often, non-drinker) were included as measured at W2 for all participants. A dichotomous measure was included representing whether the participant had at baseline mentioned an inflammation-related somatic illness (asthma, arthritis, congestive heart failure, coronary heart disease, angina, heart attack or myocardial infarction, stroke, emphysema, chronic bronchitis, liver condition, cancer or malignancy, diabetes). Unlike in the NCDS analysis, IBS and Crohn's disease were not asked about so it was not possible to include these. Also in contrast to the NCDS analysis, it was not possible to take account of early life conditions since no consistent measure of childhood conditions or social class is available for all participants in this dataset (parental RGSC at age 14 was available only for the BHPS component; the new UKHLS sample had only parental SOC codes).

6.3.1.3 Analysis

Linear regressions using imputed data were used to examine the impact of log-transformed CRP and fibrinogen on continuous GHQ one year after the nurse visit, and logistic regression using imputed data were used to examine the impact of log-transformed CRP and fibrinogen on odds of GHQ ≥3.

A base model adjusted for age, sex and GHQ at baseline. Successive models additionally adjusted for baseline SEP (RGSC and housing tenure), relevant somatic illness at baseline, and health behaviours at baseline or one year before (smoking, alcohol consumption and categorized BMI).

Using STATA's svyset command, all analyses took account of clustering by primary sampling unit and strata. To weight the analysis, ideally a longitudinal weight taking account of attrition between the nurse visit and one year later (i.e., W3 or W4 for the new UKHLS and BHPS sub-samples respectively) would have been used, but no such weights were available. On the advice of the UKHLS weights team, I instead used the longitudinal nurse visit weights from W4 for all participants. This unfortunately entailed exclusion of participants for whom baseline was W2 and outcome measured at W3 who would otherwise have been usable, but would best correct for factors determining presence or absence in the final sample due to non-random non-response.

6.3.1.3.1 Sensitivity Analyses

Sensitivity analyses investigated the impact of excluding participants taking medications which could affect inflammation or fibrinogen specifically (NSAIDs, statins, betablockers, lipid-lowering drugs for cholesterol or fibrinogen, anti-fibrolytics or haemostatics, prescribed aspirin, oral contraceptives or hormone replacement therapy), and excluding participants taking CNS medication including antidepressants (also including any participants taking medications for epilepsy or other neurological conditions). Finally, the impact was explored of considering the time of day, season, and processing time of blood samples. In contrast to equivalent analyses using NCDS data, it was not possible to examine the impact of excluding peri-menopausal women since this was not asked about at either the nurse visit or the mainstage interviews around this time.

6.3.2 Results

6.3.2.1 <u>Comparison of initial and final samples</u>

A comparison using imputed data (Table 6.7) found that participants included in final models tended to be older, of more advantaged SEP, with fewer depressive symptoms at baseline and outcome. They smoked less, drank more, typically had lower BMI, and took more anti-inflammatory medications but fewer antidepressants (all at $p<0.05$). They did not differ significantly in terms of

gender, somatic illness at baseline, or HRT/OC use. The final sample was therefore selected for good mental health and favourable economic position. Due to the exclusion of participants with CRP>10mg/L, mean levels of both inflammatory markers were lower in the final sample compared to the initial sample.

6.3.2.2 Association of inflammatory markers with GHQ one year later

Adjusting for age and sex only, CRP and fibrinogen were both significantly associated with GHQ one year later in continuous models, and CRP was associated with GHQ 3+ one year later (Table 6.8). The addition of baseline GHQ to the model substantially attenuated associations, which became non-significant except for the association with CRP in the continuous model.

Successive adjustment for SEP, relevant somatic illnesses, and health behaviours all produced further attenuation (Table 6.8). In the fully-adjusted model, associations with both CRP and fibrinogen were entirely explained, as effect sizes approached the null. Adjustment for covariates individually (Table 6.9) showed that health behaviours produced the most attenuation, followed by SEP.

Table 6.7: Characteristics of initial and final samples (UKHLS)					
		Initial sample: present at nurse visit N=20,685		Final sample* N=15,627 in m=0 N=15217-85 in imputed data	
		Unimputed	Imputed	Unimputed	Imputed
BASELINE CHARACTERISTICS		(%)	(%)	(%)	(%)
Age	15-31	16.8	16.8	13.8	13.9
	32-47	27.3	27.3	26.7	26.8
	48-64	28.5	28.5	30.4	30.3
	>65	27.4	27.4	29.2	29.0
Sex	Male	44.0	44.0	44.0	44.2
	Female	56.1	56.1	56.0	55.8
		Mean	Mean	Mean	Mean
Inflammatory markers	CRP (mg/L)	3.26*	3.23	2.07**	2.05
	Fibrinogen (g/L)	2.79[+]	2.79	2.75[++]	2.74
		(%)	(%)	(%)	(%)
SEP: housing tenure	Owns outright	35.0	35.1	37.8	37.8
	Buying w/ mortgage	39.2	39.3	39.2	39.5
	Council rented	15.0	15.1	13.7	13.5
	Private rented/other	10.6	10.6	9.2	9.2
	Missing	0.1	-	0.1	-
SEP: occupational social class	Professional	4.5	5.1	4.8	5.4
	Managerial	28.5	32.5	29.5	33.5
	Skilled non-manual	19.4	22.6	19.7	22.7
	Skilled manual	16.5	19.5	16.4	19.1
	Semi-skilled	13.1	15.8	12.8	15.0
	Unskilled	3.7	4.6	3.5	4.2
	Missing	14.3	-	13.3	-
Relevant somatic illness	No	91.6	91.6	91.6	91.7
	Yes	8.4	8.4	8.4	8.3
GHQ at baseline	0-2	69.4	76.1	70.7	77.2
	3+	21.7	24.0	20.9	22.8
	Missing	8.9	-	8.4	-
Smoking	Never smoker	40.6	41.4	41.8	42.0
	Ex-smoker	38.3	39.0	39.8	39.8
	Current, <= 10/day	9.7	9.8	9.1	9.2
	Current, 11-20/day	8.0	8.2	7.7	7.6
	Current, >20/day	1.6	1.6	1.5	1.4
	Missing	1.9	-	0.1	-
Drinking frequency	Most days	12.9	15.1	13.8	15.9
	2-3 days/week	12.9	15.2	13.7	15.8
	>1/month, < 1/week	24.9	29.8	25.4	29.6
	<1/month	29.7	36.5	29.9	35.5
	Non-drinker	2.6	3.4	2.5	3.2
	Missing	17.0	-	14.6	-
BMI	18.5-24.9	30.6	30.8	29.9	30.7
	25.0-29.9	36.8	37.2	37.8	38.5
	30-34.9	19.4	19.7	19.6	19.8
	>35	10.7	10.9	10.4	9.8
	<18.5	1.4	1.4	1.2	1.2
	Missing	1.1	-	1.0	-
Takes potentially anti-inflammatory medications	No	79.0	79.0	77.9	78.1
	Yes	21.0	21.0	22.1	21.9

Takes CNS medication	No	79.6	79.6	80.3	80.8
	Yes	20.4	20.4	19.7	19.2
HRT or OC use	No	98.4	98.4	98.3	98.3
	Yes	1.6	1.6	1.7	1.7
OUTCOME CHARACTERISTICS					
GHQ	0-2	65.5	76.1	70.7	77.2
	3+	19.7	23.9	20.9	22.8
	Missing	14.8	-	8.4	-

* Present at nurse visit and one year later, not pregnant at either point, excluding CRP>10mg/L, non-zero weights at W4

*Based on 12521 obs ** Based on 9525 obs [+]Based on 12828 obs [++]Based on 9756 observations

Table 6.8: Association of inflammatory markers with GHQ one year later (UKHLS)

CRP (log-transformed)	Linear model: GHQ one year later			Logistic Model: GHQ (3+) one year later		
	Coeff	CI	P	OR	CI	P
Crude: Age and sex	0.15	0.07-0.22	<0.001	1.09	1.03-1.16	0.004
Base model: Age, sex, baseline GHQ	0.07	0.01-0.14	0.03	1.06	0.99-1.13	0.08
Base model + SEP: housing tenure, RGSC	0.05	-0.01-0.12	0.10	1.04	0.98-1.12	0.20
Base model + SEP + relevant somatic illness	0.05	-0.01-0.12	0.12	1.04	0.97-1.11	0.24
Full: Base model + SEP + somatic illness + health behaviours	0.03	-0.04-0.10	0.38	1.02	0.95-1.10	0.52
Fibrinogen (log-transformed)	Linear model: GHQ one year later			Logistic Model: GHQ (3+) one year later		
	Coeff	CI	P	OR	CI	P
Crude: Age and sex	0.44	0.11-0.76	0.01	1.24	0.93-1.64	0.14
Base model: Age, sex, baseline GHQ	0.16	-0.11-0.43	0.25	1.08	0.81-1.44	0.62
Base model + SEP: housing tenure, RGSC	0.09	-0.18-0.36	0.49	1.02	0.76-1.36	0.90
Base model + SEP + relevant somatic illness	0.09	-0.19-0.36	0.53	1.01	0.75-1.35	0.95
Full: Base model + SEP + somatic illness + health behaviours	-0.08	-0.37-0.21	0.61	0.88	0.64-1.20	0.41

Table 6.9: Attenuation of effects with adjustment for individual covariates (UKHLS)						
Association of Inflammatory markers at 45 with Malaise Inventory at 50						
CRP (log-transformed)	Linear model: GHQ one year later			Logistic Model: GHQ (3+) one year later		
	Coeff	CI	P	OR	CI	P
Base model: Age, sex, baseline GHQ	0.07	0.01-0.14	0.03	1.06	0.99-1.13	0.08
Base model + smoking	0.05	-0.01-0.12	0.10	1.04	0.98-1.11	0.21
Base model + drinking	0.07	0.01-0.13	0.04	1.05	0.99-1.13	0.12
Base model + BMI	0.07	-0.00-0.14	0.07	1.06	0.98-1.13	0.15
Base + all health behaviours	0.04	-0.03-0.11	0.27	1.03	0.96-1.11	0.42
Base model + SEP	0.05	-0.01-0.12	0.10	1.04	0.98-1.12	0.20
Base model + somatic illness	0.07	0.00-0.13	0.04	1.06	0.99-1.13	0.11
Fibrinogen (log-transformed)	Linear model: GHQ one year later			Logistic Model: GHQ (3+) one year later		
	Coeff	CI	P	OR	CI	P
Base model: Age, sex, baseline GHQ	0.16	-0.11-0.43	0.25	1.08	0.81-1.44	0.62
Base model + smoking	0.03	-0.24-0.31	0.81	0.97	0.72-1.30	0.82
Base model + drinking	0.10	-0.17-0.38	0.45	1.02	0.76-1.37	0.88
Base model + BMI	0.12	-0.16-0.40	0.40	1.04	0.77-1.40	0.81
Base + all health behaviours	-0.07	-0.36-0.22	0.64	0.89	0.64-1.20	0.42
Base model + SEP	0.09	-0.18-0.36	0.49	1.02	0.76-1.36	0.90
Base model + somatic illness	0.15	-0.13-0.42	0.29	1.06	0.79-1.42	0.69

6.3.2.3 Sensitivity analyses

As shown in Table 6.10, exclusion of participants prescribed anti-inflammatory medications, HRT, oral contraceptives, or antidepressants did not affect conclusions; neither did addition of the season, time of day, and processing time of blood samples to either base or fully-adjusted models.

Table 6.10: Sensitivity analyses: association of inflammatory markers with GHQ one year later (UKHLS)						
CRP (log-transformed) *All estimates are fully-adjusted*	Linear model: GHQ one year later			Logistic Model: GHQ (3+) one year later		
	Coeff	CI		Coeff	CI	
Excluding participants taking anti-inflamm meds, HRT or oral contr.	0.04	-0.04,0.12	0.33	1.03	0.96,1.12	0.41
Excluding participants taking antidepressants	0.03	-0.05,0.10	0.50	1.02	0.94,1.12	0.62
Adjusting for season, time of day and processing time	0.03	-0.04,0.11	0.36	1.02	0.95,1.10	0.51
Fibrinogen (log-transformed) *All estimates are fully-adjusted*	Linear model: GHQ one year later			Logistic Model: GHQ (3+) one year later		
	Coeff	CI	P	OR	CI	P
Excluding participants taking anti-inflamm meds, HRT or oral contr.	-0.06	-0.38,0.27	0.73	0.88	0.62,1.25	0.47
Excluding participants taking antidepressants	-0.06	-0.38,0.25	0.68	0.89	0.61,1.30	0.55
Adjusting for season, time of day and processing time	-0.08	-0.37,0.21	0.57	0.87	0.63,1.19	0.38

6.4 Discussion

6.4.1 The 1958 Cohort Study

The attenuation in NCDS analyses of CRP and fibrinogen associations with adjustment for earlier depressive symptoms is consistent with a bidirectional relationship of systemic inflammation and depressive symptoms, while attenuation with adjustment for SEP and inflammation-related somatic illnesses suggests a degree of confounding or mediation by these factors.

Health behaviours emerged as an important factor in this association, although their exact role is unclear. Additional analyses, in which the most recent measurements of health behaviours were replaced with equivalent measurements from earlier sweeps, investigated whether recent changes to health behaviours shortly before baseline were affecting later depressive symptoms via inflammation. However, since substitution of earlier health behaviours did not change results at all, this hypothesis was not supported. In contrast to the reverse relationship (depressive symptoms → inflammation), it is not obvious how health behaviours could plausibly mediate associations between inflammation and depressive symptoms, since it is difficult to see how sub-clinical or systemic inflammation, in the absence of a long-term inflammatory illness, would causally influence smoking, drinking, or BMI. Nevertheless, a related explanation was considered involving confounding rather than mediation: with recent changes to smoking, drinking, and/or BMI at or before baseline affecting inflammatory markers and depressive symptoms independently, thus producing a spurious association between those two. As with the hypothesis that recent changes to health behaviours were affecting depressive symptoms via inflammation, this would also require a lag-time in the effect of health behaviours on depressive symptoms, since if both depression and inflammation were affected equally quickly one would expect elevations in MI score due to health behaviours to have already occurred at baseline, and attenuation seen earlier with adjustment for baseline MI rather than with adjustment for health behaviours themselves. However, that results barely changed with substitution of earlier health behaviours undermines confounding by recently-

changed health behaviours as much as mediation by recently-changed health behaviours as the explanation for the attenuation observed.

Is there any other way that health behaviours being 'on the causal pathway' and influencing depressive symptoms *via* inflammation could be tenable as an explanation of results seen? If – as indicated by sensitivity analyses – patterns of health behaviours are in this cohort relatively stable throughout middle age, then this hypothesis is undermined by the fact that this attenuation did not occur earlier on in the base model with adjustment for depressive symptoms at baseline. Presumably, the same health behaviours influencing depressive symptoms at 50 via inflammation would have similarly influenced depressive symptoms at 42 via inflammation, such that addition of earlier depressive symptoms to the model would have already captured and adjusted for this pathway. However: relevant here is the finding that adjustment for an average of Malaise Inventory at 33 and 42 attenuated crude associations more than adjustment simply for MI at 42 despite the fact that this measurement was much closer to baseline. This suggests that MI is a rather 'noisy' or labile measure subject to substantial short-term variation, such that that any single measurement of MI may be a relatively poor indicator of typical MI around the time it was taken. The effect of this will be to impair the extent to which including baseline MI can in fact achieve what adjustment for baseline value of the outcome in a longitudinal study is supposed to do: capturing and controlling for the myriad stable or relatively stable influences similarly acting on a measure such as depressive symptoms at both baseline and outcome, in order to isolate the association of interest (here, inflammation at 45). Considering this, the hypothesis that established (rather than recently changed) health behaviours are to some extent affecting depressive symptoms at 50 *via* inflammation at 45 becomes tenable – an interpretation well supported by the background literature linking inflammation to depressive symptoms on the one hand, and health behaviours and inflammation on the other. If this interpretation is correct, then adjustment for health behaviours as part of the final model would be incorrect, since to the extent that established health behaviours are in fact further up the causal pathway this would clearly be over-adjustment. A more appropriate final model would

perhaps be that in which only social class in childhood and at 42, MI at 42, and longterm illness at 42 are adjusted for. However, as can be seen in table 6.2, taking this approach finds only a weak and borderline significant (OR: 1.08, p=0.05) association of CRP with above-cutoff MI symptoms, and no evidence for an association of CRP with continuous MI score (coeff: 0.03, p=0.16). Hence while the pattern of attenuation in CRP models remains unexplained, none of the interpretations considered can be said to support a causal or even predictive association of systemic inflammation with later depressive symptoms in this study population.

6.4.1.1 CRP vs Fibrinogen

An unexpected result of the NCDS analysis was the discrepancy between the two inflammatory markers, with a robust predictive association of fibrinogen for Malaise Inventory but a complete lack of predictive associations for CRP. This presents at least two possible explanations.

Firstly, if we assume that the predictive association of fibrinogen is due to a causal influence of systemic inflammation on depressive symptoms, then CRP must be acting as a less accurate marker for inflammatory processes than fibrinogen. This could result from CRP being a more unstable molecule than fibrinogen, such that CRP but not fibrinogen degraded sufficiently between collection and processing of blood samples to obscure associations. To test this, CRP models were re-run restricted to participants whose processing time for blood samples was 2 days or less, but conclusions did not change (for continuous MI, coeff: -0.00, p= 0.95, OR for MI 4+: 1.01, p=0.78 in fully-adjusted models).

Alternatively, results could indicate that a process independent of systemic inflammation, and associated with fibrinogen but not CRP, is either confounding the association with MI or mediating it. Since fibrinogen is involved in haemostatic as well as inflammatory processes, this is not impossible, and that 8.4% of the sample were taking NSAIDs but only 1.5% of the sample were taking fibrates is consistent with this explanation. Another explanation may point to a limitation of the depressive symptoms measure used in the NCDS analyses: since the 9-item Malaise Inventory (unlike

the GHQ-12, used in the UKHLS) includes a number of items measuring somatic symptoms of depression, it is possible that in NCDS analyses the index of depressive symptoms is picking up an aspect of physical health independent of systemic inflammation but specifically linked to fibrinogen.

6.4.2 UKHLS

In contrast to the NCDS analyses, in the UKHLS there was no evidence at all that systemic inflammation, as indexed by either CRP or fibrinogen, predicts GHQ one year later after accounting for reverse causation and likely confounders.

Since in this population it was possible to adjust for GHQ at baseline itself as opposed to a proxy measure from two years earlier, and the sample size was both much larger and weighted to account for non-representativeness, failure to replicate the predictive association of fibrinogen seen in the NCDS suggests it may be specific to that population. Because the age distribution of this sample was much wider than the NCDS, an additional analysis restricted models to the middle two age groups (32-64 at baseline, N=8715) to see if a predictive association existed in this sub-population. Since this appeared to strengthen associations with CRP (GHQ score coeff: 0.09, p=0. 0.06, OR for GHQ 3+: 1.08, p=0.08), but not fibrinogen (GHQ score coeff: -0.04, p=0.87, OR for GHQ 3+: 0.93, p=0.72), age distribution does not appear to explain the lack of fibrinogen association in the UKHLS. Since UKHLS analyses but not NCDS analyses were weighted for non-random non-response, UKHLS analyses were re-run unweighted. This did not change conclusions either (for CRP, GHQ score coeff: 0.04, p=0.17, OR for GHQ 3+: 1.04, p=0.27; for fibrinogen, GHQ score coeff: -0.01, p=0.97, OR for GHQ 3+: 0.93, p=0.60).

It should be noted that since different mental health measures were used in the two datasets, the results may not be directly comparable. It is possible that aspects of mental health measured by the 9-item Malaise Inventory are predicted by fibrinogen to a greater extent than those aspects measured by the GHQ, as a result of its relationship with either systemic inflammation or with a separate process.

6.4.3 Support for Hypotheses

Contrary to initial hypotheses, since only fibrinogen was robustly associated with depressive symptoms and only in one of two study populations, results cannot be said to support a causal role of inflammation in depression.

6.4.4 Fit with previous research

Since only 8 of the 20 studies reviewed which examined a pathway from inflammation to depression supported a causal relationship, the lack of association seen in the NCDS and UKHLS analyses are certainly not inconsistent with previous research as whole. However, it is worth asking why no association would be seen in these populations in contrast to the 8 studies with positive results.

It is possible that methodological limitations of the NCDS analysis (a long follow-up between baseline and outcome, adjustment for a proxy measure of baseline depressive symptoms, bias due to non-random attrition in the sample) may have biased results for that population with the effect of masking a predictive association. The same cannot be said for the UKHLS analysis, which had a one-year follow-up time, directly comparable mental health measures at both time-points, and longitudinal weights to account for non-random non-response. Since the large sample had a roughly even gender composition and ranged in age from 16 to 97, the null result cannot be explained as the result of a small or unusual sample.

Another plausible source of heterogeneity is the measure of depression symptoms used. The measures used in epidemiological studies such as the Malaise Inventory and the GHQ undoubtedly differ both from clinical interviews used to diagnose depressive disorders and from one another in the underlying constructs which they aim to capture, raising the possibility that some of these constructs are more influenced by inflammation than others. Only one of the previous studies identified used the GHQ as a measure of depressive symptoms, and was one of the 8 which supported a role for inflammation in depression. However, this study in fact used a four-item

subscale of the 30-item GHQ, obtained by factor analysis, intended as a measure of cognitive symptoms of depression specifically (whether, compared to usual, participants had felt like a worthless person, felt that life is entirely hopeless, felt that life isn't worth living, or found at times they couldn't do anything due to nerves)[235]. Since the UKHLS used the 12-item version of the GHQ which does not include all four of these items, it was unfortunately not possible to examine whether use of the subscale explained the discrepancy in results. Since no other study was identified which has examined the inflammation-depression directionality using the Malaise Inventory to index depressive symptoms, it is unclear whether lack of a robust association is typical when this measure is used.

Is it also possible that predictive associations observed in animal and human laboratory studies do indeed reflect a genuine causal process whereby systemic inflammation plays a role in depressive symptomatology, but one which is sufficiently modest so as to be obscured at the population level in measurements taken months or years apart. A multitude of other processes will affect both inflammatory marker levels and depressive symptoms over the timescales of months or years typical of epidemiological investigations; health-related behaviours and social conditions will change in small ways, acute illnesses will come and go, long-term illnesses will vary in their severity, seasonal changes will impact biomarkers throughout the year, and underneath sources of cyclical variation systemic inflammation will be continually increasing as participants age. In this context it is worth considering whether the influence of inflammation on depressive symptoms may be real, but small compared to that of other deterministic factors, and the measurement error inherent to both depressive symptom questionnaires and molecules such as CRP and fibrinogen as markers of typical values around the time of measurement. It that were true, it would explain the continued inconsistency in results of epidemiological studies on this topic, despite the strong theoretical basis on which to expect a predictive association and the results of controlled laboratory studies. Results of these analyses may, therefore, indicate that any causal influence of systemic inflammation on

depression is clinically rather modest compared to other factors, and that in public health terms resources may be better spent on other avenues to tackle depression.

6.5 Chapter Summary

This analysis explored whether increases in depressive symptoms were predicted by two markers of systemic inflammation CRP and fibrinogen in two study populations, and found a robust association only for fibrinogen in the NCDS. It is unclear what is causing the discrepancy between the two inflammatory markers and between the two populations, but in any case this analysis does not support a substantial causal role for systemic inflammation in depression. Consequently, neither does it support the hypothesis that systemic inflammation mediates between unemployment and depressive symptoms, despite the higher levels of CRP and fibrinogen among unemployed study participants seen in Chapter 4. For this reason, in the final empirical chapter longitudinal associations of unemployment with depressive symptoms are explored independently of systemic inflammation, rather than attempting to link the three factors in a multi-staged process using mediation models.

7 LONGITUDINAL ANALYSIS OF UNEMPLOYMENT AND DEPRESSIVE SYMPTOMS

7.1 Chapter Overview

This chapter contains analyses relating to objective 4: investigation of longitudinal associations of past unemployment and depressive symptoms. Firstly, methods and results are presented for the NCDS, followed by methods and results for UKHLS. In the following section, both sets of results are discussed with reference to initial hypotheses and the previous literature.

It was hypothesised that:

1. Current unemployment will be strongly associated with depressive symptoms.
2. Number of depressive symptoms at follow-up will increase with increasing total aggregated unemployment.
3. Number of depressive symptoms at follow-up will increase with number of spells.
4. Depressive symptoms will be more strongly associated with more recent unemployment.
5. Depressive symptoms will be more strongly associated with unemployment spells early in life, indicating a sensitive period effect.

7.2 The 1958 Birth Cohort (NCDS)

7.2.1 A note on recentness and life periods

Since all the participants in this dataset are the same age and measurements were taken at the same time, it is impossible to completely separate the effect of the recentness of an unemployment spell from the age at which it occurred. Nevertheless, these two aspects of past unemployment were defined in such a way as to allow for some pathways to be potentially disentangled. For instance, by looking at the life period in a person's *first* unemployment spell occurred, strong scarring effects of youth unemployment – possibly mediated by later unemployment – would be indicated by stronger associations with later psychological distress for first spells occurring during the earlier periods, despite the experience being less recent. Similarly, a lack of association with a person's *last* unemployment spell unless it was very recent might indicate that psychological effects of unemployment, unless mediated through later unemployment, are not in themselves long-lasting.

7.2.2 Methods

7.2.2.1 Analytic sample

For the most part, analysis was restricted to the 9763 participants present at sweep 8 when outcome was measured, with multiple imputation (M=20) was used to fill in missingness in covariates and a small amount of missingness in outcome (1.6%) for these participants. Analyses of recentness of last unemployment excluded participants who were currently sick or disabled, since it would have been inappropriate to include these participants in the baseline 'never unemployed' group.

7.2.2.2 Measures

7.2.2.2.1 Unemployment at age 50

The summary measures calculated from the updated activity histories dataset were:

1. Total aggregated unemployment in months since age 16. Since this was highly skewed, this was categorised into 0-6 months 7-12 months, 12-36 months, and >36 months.
2. Total number of unemployment spells since age 16. This was also highly skewed, and was categorised into 0, 1, 2, and 3+.
3. Timing of first unemployment, categorised as 16-21, 21-30, 30-40, 40+
4. Most recent unemployment, categorised as: current within past 5 years (since age 45), 5-10 years ago (age 40-45), 10-20 years ago (age 30-40), 20-29 years ago (age 21-30) or >29 years ago (age 16-21).

7.2.2.2.2 Psychological distress at age 50

At age 50, psychological distress was measured by the 9-item Malaise Inventory Score (hereafter MI score) during a computer-assisted self-interview (CASI). The questions included in this version are listed in the methods chapter. For each item, participants could score 0 or 1 and the summary score was calculated. Since total score was highly skewed, it was log-transformed for analysis. A dichotomous measure was also calculated using the standard cut-off for clinically significant symptoms of 4+.

7.2.2.2.3 Internalising and externalising symptoms at age 16

At age 16, participants' mental health was measured using the Rutter Scale. Following the procedure used by Clark colleagues to adjust for early mental health in this dataset[252], five items from the parent version of the Rutter questionnaire indexing internalising (depression/anxiety) symptoms were drawn out and the square root of the subscale total calculated, and a further 9 items used to calculate an equivalent square root total of externalising symptoms. The individual items are listed in the methods chapter.

7.2.2.2.4 Longstanding illness or disability

Also included as a component of relevant initial conditions at labour market entry was whether participants already had longstanding illness or disability, either reported by the parent or as noted during the physical examination component of the survey. This could in theory include psychiatric conditions, but since only approximately 0.7% of participants classified as having a long-term condition cited a psychiatric one, this was effectively a measure of physical health at 16. At age 50, a measure of longstanding illness excluding mental health conditions was available.

7.2.2.2.5 Socioeconomic position

Socioeconomic position at labour market entry was measured by the housing tenure of participants' parents, and the occupational social class of the participants' father, when participants were aged 16. Father's social class and parental housing tenure from earlier in childhood, plus measures of overcrowding, father's education and reported financial difficulties in childhood were used as auxiliary variables to impute these. For father's social class, participants living in households with no male head or a father not in employment during this period were included as a separate group. Socioeconomic position at age 50 was indexed by participants' own housing tenure and the occupational class of their current job or else the most recent job for which this information was available.

7.2.2.2.6 Health behaviours at age 50

Smoking was assessed by self-report and classified as never smoker, ex-smoker, current (up to 10 per day), current (11-20 per day), and current (21+ per day). Frequency of alcohol consumption was assessed by self-report and classified as on most days, 2-3 days per week, once per month-once per week, less than once per month, and non-drinkers. BMI at sweep 8 was categorized using standard WHO classifications (<18.5, 18.5-24.9, 25-29.99, 30-34.99, ≥35). Since most participants did not

report their height at sweep 8, height from the biomedical wave 5 years earlier was used, together with weight as reported at sweep 8.

7.2.2.3 Multiple Imputation

The four summary unemployment variables of total unemployment in months, number of spells, age at first unemployment and recentness of last unemployment were included in imputation models along with individual malaise inventory items, all covariates, and a number of auxiliary variables such as malaise inventory items and SEP measures from earlier sweeps. Unlike the 3889 participants who dropped out prior to age 16 and consequently did not have a record in the activity histories database because one was never constructed for them, participants who dropped out between age 16 and age 50 presented a more subtle challenge, since they had partial activity history information. For these cohort members, a summary variable such as total months of unemployment calculated at age 50 would not be comparable with the equivalent summary variable for participants who remained in the study throughout. For example, a person who dropped out after sweep 5 when participants were aged 33 and had reported 4 months of unemployment prior to that point would be assigned a value of 4 months of total unemployment, this having been calculated from 17 years of data. This would be treated in an imputation model in exactly the same way as a value of 4 for a person with 4 months' reported unemployment in a complete 34-year activity history to age 50, which is clearly inappropriate. For this reason, only participants who were present at sweep 8 were included in imputation models. This meant that summary unemployment variables, while used to inform the imputation models, were not themselves imputed in this analysis.

Prior to imputation, tests for interactive effects of gender and country at sweep 8 were performed. Since interaction effects were not supported, interactions were not included in the imputation models and were not considered further.

7.2.2.4 Analyses

Linear regression was used to explore associations of lifetime unemployment with continuous MI score, and logistic regressions to explore associations of lifetime unemployment with clinically relevant depressive symptoms (an MI score of 4+).

The first model adjusted for 'initial conditions': internalizing and externalising symptoms, physical health, and SEP at 16, as well as country at outcome measurement. In subsequent models, three distinct pathways by which unemployment might impact on mental health at age 50 were explored. These were: physical health by age 50, SEP at 50, and current unemployment at 50. A final set of models adjusted for all these factors simultaneously.

7.2.2.5 Sensitivity analyses

Sensitivity analysis explored whether health behaviours (smoking, drinking and BMI) could be operating as an additional pathway by adding this block to both initial conditions and fully-adjusted models. Next, models were re-run with participants taking anti-depressant medications excluded. Finally, models were stratified by educational qualifications (dichotomized as degree or higher degree/teaching or other professional qualification/A-levels, and O-levels/apprenticeship/no qualifications) and associations examined separately in each group.

7.2.3 Results

Excluded participants differed significantly from participants retained in the final sample on all initial conditions (Table 7.1). They were less likely to be male (49.3% vs. 54.5%, $p<0.001$) and more likely to have had a longstanding illness at age 16 (10.1 vs. 8.5%, $p=0.001$). They were of less advantaged SEP as measured by father's RGSC and parental housing tenure at age 16 and scored more highly for internalising and externalising symptoms (all $p<0.001$). They did not differ significantly with respect

to country of residence at 16. The final sample was therefore selected for favourable socioeconomic position, physical and mental health at labour market entry.

Table 7.1: Characteristics of initial and final samples (NCDS)				
		Initial sample, unimputed (N=18558)	Final sample (N=9763), unimputed	Final sample (N=9763) Imputed data
		(%)	(%)	(%)
Malaise Inventory Score at age 50	0-3	55.9	84.0	85.2
	4+	9.6	14.4	14.8
	Missing	34.6	1.6	-
Sex	Female	49.4	50.8	50.8
	Male	50.6	49.2	49.2
Internalizing symptoms at 16	Mean(SD)	1.21(1.57)*	1.12(1.49)**	1.17
Externalising symptoms at 16	Mean(SD)	1.34(2.74)$^{+}$	1.12(2.45)$^{++}$	1.27
Longstanding illness/disability at 16	No	81.6	82.9	91.6
	Yes	8.0	7.6	8.4
	Missing	10.4	9.6	
SEP in childhood: parental housing tenure	Owner-occupier	36.7	39.1	51.3
	Council rented	29.2	28.2	38.8
	Private rented/other	6.7	7.1	9.9
	Missing	27.5	25.6	-
SEP in childhood: father's occupational social class	Professional	3.6	4.1	4.6
	Managerial	13.4	15.0	16.8
	Skilled non-manual	6.4	6.7	7.5
	Skilled manual	29.6	30.0	33.2
	Semi-skilled	9.6	9.3	10.3
	Unskilled	3.6	3.1	3.4
	No male head/father not in work/forces	22.6	21.5	24.1
	Missing	11.2	10.4	-
Qualifications at 23	Degree	6.8	9.7	11.2
	Teacher, nurse etc.	5.7	7.9	9.1
	A levels	11.1	15.2	17.7
	O-levels or less	23.1	29.9	35.2
	Apprentice/other	2.0	2.4	2.9
	None	18.8	19.9	24.0
	Missing	32.4	15.0	-
Longstanding illness/disability at 50	No	46.2	69.4	69.6
	Yes	20.2	30.4	30.4
	Missing	33.6	0.2	-
Housing tenure at 50	Owns outright	15.9	24.0	24.0
	Buying (mortgage)	39.3	59.0	59.1
	Council rented	6.0	9.0	9.0
	Pvt renting/other	5.2	7.9	7.9
	Missing	33.6	0.2	-
Occupational social class at 50 from current or last employment	Professional	3.9	5.9	5.9
	Managerial	26.2	39.4	39.6
	Skilled non-manual	12.7	19.1	19.2
	Skilled manual	13.1	19.8	19.9
	Semi-skilled	7.9	11.9	12.0
	Unskilled	2.3	3.4	3.4
	Missing	33.9	0.6	
Smoking at 50	Never smoker	30.7	46.1	46.3
	Ex-smoker	20.5	30.9	31.0
	Current, <=10/day	6.2	9.2	9.3

	Current, 11-20/day	7.1	10.7	10.7
	Current, 21+/day	1.8	2.7	2.7
	Missing	33.8	0.5	-
Drinking frequency at 50	Most days	12.1	22.9	23.0
	2-3 days/week	16.2	30.7	30.8
	1/week or less	20.9	39.6	39.8
	Non-drinker	3.3	6.3	6.4
	Missing	47.5	0.5	
BMI at 50	18.5-24.9	17.9	27.0	32.9
	25.0-29.9	21.4	32.2	39.5
	30.0-34.9	9.3	14.0	18.0
	>35.0	4.1	6.2	8.7
	<18.5	0.4	0.6	0.9
	Missing	46.8	20.1	-
Country of residence at 50	England	56.5	85.0	85.0
	Wales	3.7	5.5	5.6
	Scotland	6.3	9.5	9.5
	Missing	33.5	85.0	-
*Based on 12,271 obs **Based on 7489 obs $^{+}$Based on 12,138 obs $^{++}$Based on 7436 obs				

Table 7.2: Unemployment summary variables, final sample (NCDS)

		Final sample: N=9763
		(%)
Total unemployment (months) age 16-50	Never unemployed	62.2
	Up to 6 months	16.6
	6-12 months	7.3
	13-36 months	8.0
	37+ months	6.0
Number of unemployment spells	Never unemployed	62.2
	1	22.2
	2	8.2
	3 or more	7.5
Timing of first unemployment	Never unemployed	62.2
	16-21	12.5
	21-30	15.0
	30-40	5.9
	40+	4.5
Timing of most recent unemployment	Never unemployed	62.2
	Current	2.6
	Ended 45-50 (<5 years ago)	4.0
	Ended 40-45 (5-10 years ago)	3.5
	Ended 30-40 (10-20 years ago)	8.6
	Ended 21-30 (20-29 years ago)	13.0
	Ended 16-21 (29+ years ago)	6.1

7.2.3.1 Total unemployment in months, 16-50

Adjusting for sex and country, a stepwise association was seen between total years of unemployment and Malaise Inventory Score in both linear and logistic models, with greater elevations in both total MI score and odds of above-cut-off score for participants who had experienced more unemployment and significant elevations for the top two groups (1-3 years and 3+ years) (Table 7.3). This pattern was robust to adjustment for initial conditions. While some attenuation occurred, supporting the operation of selection processes in this relationship, in models adjusting for initial conditions a stepwise pattern remained with greater elevations in both total MI score and odds of above-cut-off score for participants who had experienced more unemployment, and substantial and significant elevations for the top two groups (Table 7.3).

In models exploring mediation pathways, the greatest attenuation resulted from inclusion of SEP at age 50. Smaller changes resulted from inclusion of long-term physical health conditions and current unemployment. As in the initial conditions models, stepwise associations were visible for both the continuous and binary outcomes, with effects were greater for 3+ years than 1-3 years.

In the full model including initial conditions and all mediation pathways simultaneously, elevations in total MI attenuated substantially, while associations with odds of 4+ MI score appeared largely explained.

7.2.3.2 Number of unemployment spells 16-50

A very similar pattern was observed for the number of unemployment spells experienced (Table 7.4). Adjusted for sex and country, both linear and logistic models showed significant and stepwise associations between number of unemployment spells and Malaise Inventory at 50. With adjustment for initial conditions, attenuation occurred for the top group (3+ spells), but associations for all groups were robust. Of potential mediators, SEP at 50 produced the most attenuation, such that associations with odds of above-cutoff MI appeared largely explained for the top group (3+

spells) although not the middle group (2 spells). In the full model, associations with both outcomes were attenuated although not entirely explained for the middle group of 2 spells.

7.2.3.3 Timing of first unemployment

Adjusting for initial conditions, first unemployment at all ages was associated with significant elevations in total MI score compared to participants never unemployed, with the strongest associations for first unemployment before age 21 or after 40 (Table 7.5). This pattern was also seen for the dichotomous outcome, although associations were not significant for all groups.

Adjustment for SEP at 50 again produced the most attenuation, with the exception of adjustment for current unemployment for participants whose first unemployment spell had begun since age 40 (unsurprisingly, since these spells would be most likely to be ongoing). Throughout, the strongest associations were seen with first unemployment at ages 16-21, which were not entirely explained even in fully-adjusted models.

7.2.3.4 Recentness of last unemployment

This analysis confirmed the strong association between current unemployment and depressive symptoms, with both total MI and odds of MI 4+ significantly and substantially higher for the currently unemployed than any other group at every level of adjustment (Table 7.6). Smaller associations were seen of total MI score with unemployment within the past five years and 5-10 years ago which were robust to adjustment for initial conditions. SEP at age 50 led to greater attenuation than long-term illness at age 50. In fully-adjusted models, associations with past unemployment <5 and 5-10 years ago were largely explained, in contrast to robust and substantial associations with current unemployment.

Table 7.3: Association of total unemployment with depressive symptoms at age 50, NCDS (N=9763) *Reference group for all analyses is participants never unemployed*								
ADJUSTMENT LEVEL	Malaise Inventory Score, 0-9				Above cut-off (4+) Malaise Inventory			
		Coeff	CI	p		OR	CI	p
Sex + country	Up to 6 months	0.13	0.02,0.23	0.02	Up to 6 months	1.15	0.98,1.34	0.07
	6-12 months	0.12	-0.03,0.27	0.126	6-12 months	1.00	0.80,1.27	0.97
	1-3 years	0.28	0.14,0.43	<0.001	1-3 years	1.44	1.17,1.76	<0.001
	> 3 years	0.85	0.68,1.02	<0.001	> 3 years	2.28	1.85,2.82	<0.001
Initial Conditions: Sex + internalising and externalising symptoms + longterm illness + SEP at 16, country at 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.13	0.03,0.24	0.01	Up to 6 months	1.17	1.00,1.37	0.06
	6-12 months	0.11	-0.04,0.26	0.15	6-12 months	1.00	0.79,1.26	0.99
	1-3 years	0.23	0.08,0.37	0.002	1-3 years	1.35	1.10,1.65	0.01
	> 3 years	0.65	0.48,0.82	<0.001	> 3 years	1.81	1.45,2.26	<0.001
SEP pathway: Initial conditions + country and SEP at 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.13	0.03,0.23	0.01	Up to 6 months	1.17	1.00,1.38	0.04
	6-12 months	0.06	-0.08,0.21	0.40	6-12 months	0.94	0.74,1.19	0.60
	1-3 years	0.15	0.00,0.29	0.04	1-3 years	1.23	1.00,1.52	0.05
	> 3 years	0.29	0.12,0.46	0.001	> 3 years	1.25	0.99,1.57	0.06
Physical health pathway: Initial conditions + country and physical health at 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.12	0.01,0.22	0.03	Up to 6 months	1.15	0.98,1.35	0.08
	6-12 months	0.09	-0.06,0.24	0.23	6-12 months	0.98	0.77,1.24	0.85
	1-3 years	0.20	0.05,0.34	0.01	1-3 years	1.31	1.06,1.61	0.01
	> 3 years	0.63	0.46,0.79	<0.001	> 3 years	1.78	1.42,2.22	<0.001
Current unemployment pathway: Initial conditions + country and current unemployment at 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.11	0.00,0.21	0.05	Up to 6 months	1.13	0.97,1.33	0.13
	6-12 months	0.08	-0.07,0.23	0.30	6-12 months	0.96	0.76,1.22	0.75
	1-3 years	0.19	0.05,0.34	0.01	1-3 years	1.29	1.04,1.58	0.02
	> 3 years	0.53	0.35,0.70	<0.001	> 3 years	1.57	1.24,1.98	<0.001
Full model: Initial Conditions + country + physical health, SEP, unemployment at 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.10	-0.00,0.20	0.06	Up to 6 months	1.13	0.96,1.33	0.13
	6-12 months	0.02	-0.12,0.17	0.77	6-12 months	0.89	0.70,1.13	0.34
	1-3 years	0.09	-0.05,0.23	0.21	1-3 years	1.16	0.94,1.43	0.18
	> 3 years	0.19	0.01,0.36	0.04	> 3 years	1.09	0.85,1.40	0.48
SA: Initial conditions + smoking, drinking and BMI at age 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.14	0.03,0.24	0.01	Up to 6 months	1.18	1.01,1.39	0.04
	6-12 months	0.07	-0.08,0.22	0.33	6-12 months	0.96	0.76,1.21	0.72
	1-3 years	0.17	0.03,0.32	0.02	1-3 years	1.28	1.04,1.57	0.02
	> 3 years	0.51	0.35,0.68	<0.001	> 3 years	1.59	1.27,1.99	<0.001
SA: Full + smoking, drinking and BMI at age 50		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.10	-0.00,0.20	0.06	Up to 6 months	1.14	0.97,1.34	0.12
	6-12 months	0.00	-0.15,0.15	0.99	6-12 months	0.86	0.67,1.10	0.22
	1-3 years	0.06	-0.08,0.20	0.38	1-3 years	1.12	0.91,1.39	0.29
	> 3 years	0.13	-0.04,0.31	0.14	> 3 years	1.03	0.81,1.33	0.79

Table 7.4: Association of number of unemployment episodes with depressive symptoms at age 50, NCDS (N=9763)
Reference group for all analyses is participants never unemployed

ADJUSTMENT LEVEL	Malaise Inventory Score, 0-9				Above cut-off (4+) Malaise Inventory			
Sex + Country		Coeff	CI	p		OR	CI	p
	1	0.16	0.07,0.26	0.001	1	1.17	1.02,1.35	0.03
	2	0.35	0.21,0.49	<0.001	2	1.56	1.28,1.89	<0.001
	3+	0.51	0.36,0.66	<0.001	3+	1.60	1.30,1.98	<0.001
Initial Conditions: Sex + country+ internalising symptoms + longterm illness + SEP at 16		Coeff	CI	p		OR	CI	p
	1	0.14	0.04,0.23	0.004	1	1.14	0.99,1.31	0.07
	2	0.32	0.18,0.46	<0.001	2	1.51	1.24,1.84	<0.001
	3+	0.39	0.24,0.54	<0.001	3+	1.39	1.12,1.72	0.003
SEP pathway: Initial conditions + country, SEP at 50		Coeff	CI	p		OR	CI	p
	1	0.10	0.00,0.19	0.05	1	1.08	0.94,1.25	0.28
	2	0.24	0.09,0.38	0.001	2	1.38	1.13,1.69	0.002
	3+	0.19	0.04,0.34	0.01	3+	1.11	0.89,1.39	0.35
Physical health pathway: Initial conditions + country, physical health at 50		Coeff	CI	p		OR	CI	p
	1	0.13	0.03,0.22	0.01	1	1.13	0.98,1.31	0.09
	2	0.29	0.15,0.43	<0.001	2	1.48	1.21,1.81	<0.001
	3+	0.34	0.19,0.49	<0.001	3+	1.33	1.07,1.65	0.01
Current unemployment pathway: Initial conditions + country, current unemployment at 50		Coeff	CI	p		OR	CI	p
	1	0.11	0.01,0.20	0.03	1	1.10	0.95,1.27	0.20
	2	0.26	0.12,0.40	<0.001	2	1.40	1.15,1.72	0.001
	3+	0.30	0.14,0.45	<0.001	3+	1.24	0.99,1.55	0.06
Full model: Initial Conditions + country, physical health, SEP, unemployment at 50		Coeff	CI	p		OR	CI	p
	1	0.06	-0.03,0.16	0.18	1	1.04	0.90,1.21	0.57
	2	0.17	0.03,0.31	0.02	2	1.28	1.04,1.57	0.02
	3+	0.09	-0.06,0.25	0.23	3+	0.98	0.78,1.24	0.88
SA: Initial conditions + smoking, drinking and BMI at age 50		Coeff	CI	p		OR	CI	p
	1	0.12	0.03,0.21	0.01	1	1.12	0.97,1.30	0.11
	2	0.27	0.13,0.41	<0.001	2	1.44	1.18,1.77	<0.001
	3+	0.30	0.15,0.45	<0.001	3+	1.28	1.03,1.59	0.03
SA: Full + smoking, drinking and BMI at age 50		Coeff	CI	P		OR	CI	p
	1	0.06	-0.04,0.15	0.24	1	1.03	0.89,1.20	0.65
	2	0.15	0.01,0.29	0.04	2	1.25	1.01,1.53	0.04
	3+	0.06	-0.09,0.21	0.45	3+	0.94	0.75,1.19	0.63

Table 7.5: Association of earliest unemployment spell with depressive symptoms at age 50, NCDS (N=9763) *Reference group for all analyses is participants never unemployed*								
ADJUSTMENT LEVEL	Malaise Inventory Score, 0-9				Above cut-off (4+) Malaise Inventory			
Initial Conditions: Sex + internalising symptoms + longterm illness + SEP at 16, country		Coeff	CI	p		OR	CI	p
	16-21	0.38	0.26,0.50	<0.001	16-21	1.54	1.31,1.82	<0.001
	21-30	0.14	0.03,0.25	0.01	21-30	1.11	0.94,1.31	0.22
	30-40	0.31	0.15,0.48	<0.001	30-40	1.38	1.09,1.74	0.01
	40+	0.33	0.14,0.52	<0.001	40+	1.39	1.07,1.80	0.02
Initial Conditions: Sex + internalising symptoms + longterm illness + SEP at 16, country		Coeff	CI	p		OR	CI	p
	16-21	0.29	0.17,0.41	<0.001	16-21	1.40	1.18,1.65	<0.001
	21-30	0.14	0.03,0.26	0.01	21-30	1.13	0.95,1.34	0.15
	30-40	0.24	0.07,0.40	0.01	30-40	1.27	1.00,1.60	0.05
	40+	0.29	0.10,0.48	0.002	40+	1.30	1.00,1.70	0.05
SEP pathway: Initial conditions + country, SEP at 50		Coeff	CI	p		OR	CI	p
	16-21	0.20	0.08,0.32	0.001	16-21	1.26	1.07,1.50	0.01
	21-30	0.09	-0.02,0.20	0.10	21-30	1.07	0.90,1.27	0.47
	30-40	0.12	-0.04,0.28	0.16	30-40	1.10	0.87,1.41	0.42
	40+	0.20	0.01,0.38	0.04	40+	1.16	0.89,1.53	0.28
Physical health pathway: Initial conditions + country, physical health at 50		Coeff	CI	p		OR	CI	p
	16-21	0.25	0.13,0.37	<0.001	16-21	1.35	1.14,1.59	0.001
	21-30	0.14	0.03,0.25	0.01	21-30	1.14	0.96,1.35	0.14
	30-40	0.22	0.05,0.38	0.01	30-40	1.24	0.98,1.57	0.08
	40+	0.27	0.08,0.45	0.001	40+	1.28	0.98,1.67	0.08
Current unemployment pathway: Initial conditions + country, current unemp at 50		Coeff	CI	p		OR	CI	p
	16-21	0.26	0.14,0.38	<0.001	16-21	1.34	1.13,1.59	0.001
	21-30	0.12	0.01,0.23	0.03	21-30	1.09	0.92,1.30	0.30
	30-40	0.18	0.01,0.34	0.03	30-40	1.17	0.92,1.49	0.20
	40+	0.09	-0.11,0.29	0.37	40+	1.03	0.77,1.37	0.86
Full model: Initial Conditions + country, physical health, SEP, unemployment at 50		Coeff	CI	p		OR	CI	p
	16-21	0.15	0.03,0.26	0.02	16-21	1.18	0.99,1.40	0.06
	21-30	0.07	-0.03,0.18	0.18	21-30	1.04	0.88,1.24	0.63
	30-40	0.06	-0.10,0.22	0.45	30-40	1.02	0.80,1.30	0.88
	40+	0.03	-0.16,0.22	0.75	40+	0.97	0.72,1.29	0.82
		Coeff	CI	p		OR	CI	p
SA: Initial conditions + smoking, drinking and BMI at age 50	16-21	0.25	0.13,0.36	<0.001	16-21	1.34	1.13,1.59	0.001
	21-30	0.12	0.02,0.23	0.03	21-30	1.11	0.94,1.32	0.22
	30-40	0.16	0.00,0.33	0.05	30-40	1.17	0.92,1.49	0.19
	40+	0.27	0.08,0.45	0.01	40+	1.28	0.97,1.67	0.08
SA: Full + smoking, drinking and BMI at age 50		Coeff	CI	p		OR	CI	p
	16-20	0.13	0.01,0.24	0.03	16-20	1.16	0.98,1.38	0.09
	21-29	0.06	-0.04,0.17	0.25	21-29	1.03	0.86,1.23	0.74
	30-39	0.03	-0.13,0.19	0.72	30-39	0.98	0.77,1.26	0.81
	40+	0.03	-0.16,0.22	0.76	40+	0.97	0.72,1.29	0.81

Table 7.6: Association of earliest unemployment spell with depressive symptoms at age 50, NCDS (N=9763) *Reference group: participants never unemployed and not currently sick/disabled*							
ADJUSTMENT LEVEL		Malaise Inventory Score, 0-9			Above cut-off (4+) Malaise Inventory		
Sex + country		Coeff	CI	p	OR	CI	P
	Current	1.20	0.97,1.43	<0.001	3.63	2.71,4.88	<0.001
	Ended 45-50 (<5 yrs ago)	0.36	0.17,0.55	<0.001	1.28	0.93,1.75	0.13
	Ended 40-45 (5-10 yrs ago)	0.30	0.09,0.50	0.004	1.31	0.93,1.83	0.12
	Ended 30-40 (10-20 yrs ago)	0.19	0.05,0.33	0.01	1.22	0.96,1.53	0.10
	Ended 21-30 (20-29 yrs ago)	0.10	-0.01,0.21	0.09	1.08	0.89,1.31	0.46
	Ended 16-21 (29+ yrs ago)	0.20	0.05,0.36	0.01	1.32	1.03,1.68	0.03
Initial Conditions: Sex + internalising symptoms + longterm illness + SEP at 16, country		Coeff	CI	p	OR	CI	P
	Current	1.11	0.87,1.34	<0.001	3.24	2.39,4.38	<0.001
	Ended 45-50 (<5 yrs ago)	0.30	0.11,0.49	0.002	1.18	0.86,1.62	0.31
	Ended 40-45 (5-10 yrs ago)	0.26	0.05,0.46	0.01	1.23	0.88,1.73	0.23
	Ended 30-40 (10-20 yrs ago)	0.15	0.01,0.29	0.03	1.16	0.92,1.46	0.22
	Ended 21-30 (20-29 yrs ago)	0.10	-0.01,0.21	0.09	1.09	0.89,1.32	0.41
	Ended 16-21 (29+ yrs ago)	0.17	0.02,0.33	0.03	1.27	0.99,1.63	0.06
SEP pathway: Initial conditions + country, SEP at 50		Coeff	CI	p	OR	CI	P
	Current	0.93	0.69,1.16	<0.001	2.65	1.94,3.61	<0.001
	Ended 45-50 (<5 yrs ago)	0.19	0.00,0.38	0.04	1.01	0.73,1.40	0.93
	Ended 40-45 (5-10 yrs ago)	0.17	-0.03,0.37	0.10	1.10	0.78,1.55	0.59
	Ended 30-40 (10-20 yrs ago)	0.10	-0.04,0.23	0.17	1.09	0.86,1.38	0.49
	Ended 21-30 (20-29 yrs ago)	0.09	-0.02,0.21	0.10	1.08	0.89,1.31	0.44
	Ended 16-21 (29+ yrs ago)	0.15	-0.00,0.31	0.05	1.24	0.96,1.59	0.09
Physical health pathway: Initial conditions + country, physical health at 50		Coeff	CI	p	OR	CI	P
	Current	1.08	0.85,1.31	<0.001	3.14	2.31,4.26	<0.001
	Ended 45-50 (<5 yrs ago)	0.27	0.09,0.46	0.004	1.15	0.83,1.57	0.42
	Ended 40-45 (5-10 yrs ago)	0.23	0.02,0.43	0.03	1.19	0.84,1.67	0.32
	Ended 30-40 (10-20 yrs ago)	0.15	0.01,0.28	0.04	1.16	0.92,1.47	0.22
	Ended 21-30 (20-29 yrs ago)	0.09	-0.02,0.20	0.11	1.08	0.89,1.31	0.44
	Ended 16-21 (29+ yrs ago)	0.16	0.01,0.31	0.04	1.25	0.98,1.61	0.07
Full model: Initial Conditions + country, physical health and SEP at 50		Coeff	CI	p	OR	CI	P
	Current	0.90	0.67,1.14	<0.001	2.59	1.89,3.54	<0.001
	Ended 45-50 (<5 yrs ago)	0.17	-0.02,0.36	0.08	0.99	0.72,1.37	0.96
	Ended 40-45 (5-10 yrs ago)	0.15	-0.06,0.35	0.16	1.07	0.75,1.50	0.72
	Ended 30-40 (10-20 yrs ago)	0.09	-0.04,0.23	0.19	1.09	0.86,1.38	0.48
	Ended 21-30 (20-29 yrs ago)	0.09	-0.02,0.20	0.12	1.07	0.88,1.31	0.48
	Ended 16-21 (29+ yrs ago)	0.14	-0.01,0.30	0.07	1.22	0.95,1.57	0.11
SA: Initial conditions + smoking, drinking and BMI at age 50		Coeff	CI	p	OR	CI	P
	Current	1.07	0.84,1.30	<0.001	3.12	2.30,4.24	<0.001
	Ended 45-50 (<5 yrs ago)	0.27	0.08,0.46	0.01	1.14	0.82,1.56	0.44
	Ended 40-45 (5-10 yrs ago)	0.23	0.02,0.43	0.03	1.17	0.83,1.66	0.36
	Ended 30-40 (10-20 yrs ago)	0.11	-0.02,0.25	0.11	1.11	0.88,1.40	0.39
	Ended 21-30 (20-29 yrs ago)	0.09	-0.02,0.20	0.12	1.08	0.89,1.32	0.43
	Ended 16-21 (29+ yrs ago)	0.16	0.01,0.31	0.04	1.25	0.98,1.60	0.08
SA: Full + smoking, drinking and BMI at age 50		Coeff	CI	p	OR	CI	P
	Current	0.90	0.67,1.13	<0.001	2.61	1.91,3.58	<0.001
	Ended 45-50 (<5 yrs ago)	0.16	-0.03,0.35	0.09	0.99	0.72,1.37	0.95
	Ended 40-45 (5-10 yrs ago)	0.14	-0.07,0.34	0.19	1.04	0.74,1.47	0.82
	Ended 30-40 (10-20 yrs ago)	0.07	-0.07,0.21	0.32	1.06	0.84,1.34	0.62
	Ended 21-30 (20-29 yrs ago)	0.08	-0.03,0.19	0.16	1.07	0.88,1.30	0.52
	Ended 16-21 (29+ yrs ago)	0.14	-0.02,0.29	0.08	1.21	0.94,1.56	0.14

7.2.3.5 Sensitivity analyses

7.2.3.5.1 Health behaviours

Sensitivity analyses indicated that health behaviours at age 50, when added either to the initial conditions or the fully adjusted stage, did not make a substantial difference to associations in any of the four analyses (Tables 7.3, 7.4, 7.5, 7.6).

7.2.3.5.2 Sensitive periods vs. accumulation

To test whether the stronger association with first unemployment at 16-21 was best explained by a sensitive period effect, or simply reflected the importance of total aggregated unemployment (which we would expect to be greater for participants who were unemployed for the first time earlier), an additional initial-conditions model included both age of first unemployment and total unemployment simultaneously. Because the baseline group of participants never unemployed was identical for both covariates, leading to extreme collinearity, this model was restricted to participants who had experienced some unemployment. This showed that after adjusting for total aggregated unemployment, the age at which this first occurred did not significantly affect the impact on MI. In contrast, after adjusting for the age at which unemployment first occurred a stepwise association with total unemployment was still seen. Compared to the group unemployed for less than 6 months, effects for the 1-3 years group were 0.12 ($p=0.16$) and 1.18 ($p=0.17$) for total and dichotomised MI respectively, and effects for the >3 years group were 0.57 ($p<0.001$) and 1.64($p<0.001$). The lack of significance for intermediate groups is consistent with the much smaller group size compared to the main analysis, since only 3695 participants experienced some unemployment.

7.2.3.5.3 Confounding by education

To examine whether associations with first unemployment at 16-21 and/or total aggregated unemployment in fact reflected the impact of leaving full-time education prior to gaining higher qualifications (remaining in full-time education through university would for the most part remove opportunity for unemployment as such at this age, potentially confounding the association) a sensitivity analysis was conducted (Table 7.7). Models were stratified by participants' highest qualification at age 23 (dichotomized as degree or higher degree/teaching or other professional qualification/A-levels, and O-levels/apprenticeship/no qualifications), and showed that predictive associations remained in both groups.

Table 7.7: Stratified by education: Association of earliest unemployment spell with depressive symptoms at age 50, adjusted for initial conditions, NCDS (N=9763)

ADJUSTMENT LEVEL		Malaise Inventory Score, 0-9			Above cut-off (4+) Malaise Inventory		
Total aggregated unemployment: Higher Qualifications		Coeff	CI	P	OR	CI	P
	<=6 months	0.24	0.09,0.38	0.001	1.40	1.06,1.86	0.02
	6-12 months	0.22	0.01,0.44	0.05	1.28	0.83,1.96	0.27
	1-3 years	0.25	0.02,0.48	0.04	1.66	1.09,2.52	0.02
	> 3 years	0.31	-0.02,0.65	0.07	1.16	0.59,2.27	0.68
Total aggregated unemployment: Apprenticeship, O-levels or less		Coeff	CI	P	OR	CI	P
	<=6 months	0.07	-0.08,0.22	0.38	1.08	0.89,1.32	0.44
	6-12 months	0.04	-0.17,0.25	0.71	0.90	0.67,1.20	0.46
	1-3 years	0.19	-0.01,0.38	0.06	1.21	0.95,1.54	0.12
	> 3 years	0.68	0.47,0.89	<0.001	1.81	1.42,2.30	<0.001
Number of spells: Higher Qualifications		Coeff	CI	P	OR	CI	P
	1	0.20	0.06,0.34	0.01	1.30	0.99,1.71	0.06
	2	0.37	0.16,0.58	0.001	1.87	1.30,2.70	0.001
	3+	0.24	0.00,0.48	0.05	1.16	0.71,1.90	0.55
Number of spells: Apprenticeship, O-levels or less		Coeff	CI	P	OR	CI	P
	1	0.10	-0.03,0.23	0.14	1.08	0.91,1.28	0.36
	2	0.27	0.07,0.46	0.001	1.34	1.05,1.71	0.02
	3+	0.42	0.22,0.62	<0.001	1.40	1.09,1.79	0.01
Age at first unemployment: Higher Qualifications		Coeff	CI	P	OR	CI	P
	16-21	0.27	0.08,0.46	0.01	1.53	1.07,2.18	0.02
	21-30	0.21	0.07,0.36	0.01	1.33	1.00,1.78	0.05
	30-40	0.30	0.03,0.58	0.03	1.44	0.86,2.41	0.16
	40+	0.24	-0.05,0.53	0.10	1.34	0.75,2.40	0.32
Age at first unemployment: Apprenticeship, O-levels or less		Coeff	CI	P	OR	CI	P
	16-21	0.27	0.11,0.42	<0.001	1.32	1.09,1.59	0.01
	21-30	0.11	-0.05,0.27	0.19	1.06	0.85,1.31	0.62
	30-40	0.18	-0.03,0.39	0.10	1.18	0.90,1.54	0.24
	40+	0.28	0.02,0.53	0.03	1.25	0.91,1.70	0.17
Recentness of last unemployment: Higher Qualifications		Coeff	CI	P	OR	CI	P
	Current	0.84	0.40,1.28	<0.001	3.16	1.61,6.22	<0.001
	Aged 45-50 (<5 yrs ago)	0.31	0.02,0.60	0.04	1.23	0.65,2.30	0.52
	Aged 40-45 (5-10 yrs ago)	0.02	-0.30,0.35	0.89	0.79	0.34,1.82	0.58
	Aged 30-40 (10-20 yrs ago)	0.25	0.03,0.47	0.02	1.42	0.92,2.21	0.11
	Aged 21-30 (20-29 yrs ago)	0.16	0.01,0.32	0.04	1.29	0.94,1.78	0.12
	Aged 16-21 (29+ yrs ago)	0.21	-0.04,0.46	0.11	1.38	0.84,2.28	0.21
Recentness of last unemployment: Apprenticeship, O-levels or less		Coeff	CI	P	OR	CI	P
	Current	1.16	0.87,1.46	<0.001	3.13	2.21,4.43	<0.001
	Aged 45-50 (<5 yrs ago)	0.27	0.02,0.53	0.04	1.13	0.78,1.65	0.53
	Aged 40-45 (5-10 yrs ago)	0.35	0.08,0.62	0.01	1.35	0.92,1.99	0.13
	Aged 30-40 (10-20 yrs ago)	0.09	-0.10,0.27	0.35	1.04	0.79,1.38	0.76
	Aged 21-30 (20-29 yrs ago)	0.07	-0.10,0.23	0.41	1.00	0.77,1.30	1.00
	Aged 16-21 (29+ yrs ago)	0.14	-0.07,0.34	0.19	1.21	0.90,1.61	0.21

7.3 Analyses using Understanding Society

7.3.1 Methods

7.3.1.1 Analytic sample

While the BHPS began in 1991, a high rate of attrition means that only 1625 participants present and of working age in 1991 were still present as of UKHLS wave 3. Since these numbers are clearly insufficient for meaningful analyses, this longitudinal component focused on a 10-year exposure period between 2001 and 2011, to allow analysis of 5687 people of working age in 2001 and continuously present between 2001 and the UKHLS wave 3.

This initial sample used for imputation models therefore contained all members of the BHPS component of the UKHLS who were present in 2001 who would later be eligible for inclusion at UKHLS wave 3 (N=17344). Multiple imputation using chained equations was used to fill in missing data within this baseline sample. Analysis models were restricted, post-imputation, to the 14,447 participants of working age (15-64) in 2001, and longitudinal weights applied to further account for non-random attrition between baseline and outcome. Because participants who had skipped waves between 2001 and 2011 were assigned longitudinal weights of zero, analysis models were effectively restricted to participants continuously present across the ten-year period.

Because of the well-known association of depressive symptoms with current unemployment, confirmed by preliminary analyses within this dataset, it was also decided to also exclude from analyses participants who had been currently unemployed when baseline depressive symptoms were measured, resulting in a final sample size which varied from 5514 to 5520 across imputations for analyses of total unemployment in months. As with the NCDS data, analyses of recentness of last unemployment excluded participants who were currently sick or disabled, since it would have been inappropriate to include these participants in the baseline 'never unemployed' group.

7.3.1.2 Measures

7.3.1.2.1 Unemployment in 2011

For this study population, past unemployment in 2011 was operationalised in the following ways: total months of unemployment over the study period (categorised into never unemployed, 1-6 months, 7-12 months, 13-24 months, >24 months) and recentness of the last unemployment spell (current, since 2006, 2001-2006, or not unemployed during the 10-year period). In contrast to analyses using the 1958 Birth Cohort, imputation of the employment history information meant it was not possible to examine the number of spells in addition to total months of unemployment due to the imputation process used. Also in contrast to the 1958 Birth Cohort, it was not possible to study the impact of the timing of person's first experience of unemployment because full employment histories since labour market entry were not available for these participants.

As described in more detail in the methods chapter, summary unemployment variables were derived from considering all current and past spells ever reported by BHPS participants between 2001 and 2011. In contrast to inflammatory markers, depressive symptoms in 2011 were measured at the mainstage (as opposed to nurse) interview itself, so unemployment during the first five months of the 2012 wave was not counted when deriving measures of past and current unemployment for GHQ analyses.

7.3.1.2.2 Depressive symptoms

Depressive symptoms were in this analysis measured by the 12-item General Health Questionnaire (GHQ) at both baseline and outcome; individual items are listed in the methods chapter. As is standard for this measure, Likert scoring was used to convert scores of 0-3 for 'not at all' to 'much more than usual' to a continuous 12-point score. This was then modelled as both a continuous

outcome and as a binary measure using the standard cut-off of ≥3, in each case adjusted for the equivalent measure in 2001.

7.3.1.2.3 Covariates at baseline and outcome

The analytic strategy involved adjustment for 'initial conditions' at baseline in all models and further exploration of mediating pathways. Initial conditions as of 2001 included age and sex, occupational social class from most recent employment (RGSC), housing tenure (owns outright, buying with mortgage council rented, private rented, other), and GHQ at baseline. Finally, a measure of self-rated health at baseline (excellent/good/fair/poor) was included, since information on specific long-standing health conditions from around this time was not available. In mediation models the following covariates were included from 2011: occupational social class from most recent employment, housing tenure, presence of a long-term illness, and current employment status in 2011. Sensitivity analyses were used to explore the impact of including health behaviours (smoking, BMI, and alcohol consumption) in 2001 and 2011, and also antidepressant use in 2011.

7.3.1.3 Multiple Imputation

Multiple imputations using chained equations (M=20) were performed on all participants present at baseline from the initial UK, Scottish, Welsh, and Northern Irish samples. The imputation models contained item-level GHQ information from 2001 and 2011, unemployment variables, all covariates used in analysis models, antidepressant use, and health behaviours for sensitivity analyses and a few auxiliary variables (height, weight, and self-rated health in 2006).

The summary variables of unemployment in this analysis were calculated from hundreds of variables corresponding to 100 current and past activity slots between 2001 and UKHLS wave 3 in 2011, and it was therefore not computationally feasible to impute these root variables individually. However, imputing the summary variables themselves would treat inappropriately the 7820 participants present in 2011 who had gaps in their employment history information (in 92.1% of cases due to

dropout prior to 2011; the remainder had skipped waves before re-entering). For a person who dropped out after 8 years but had 16 months of reported unemployment prior to dropout, the simple addition of unemployment spells would give a value for the summary variable identical to a person who was present continuously and reported 16 months unemployment across a 10-year period. This is incorrect, since it ignores the fifth of their employment history of unknown composition. On the other hand, treating the summary variable as a missing value would fail to use the partial information, and possibly lead to imputed values which we know to be incorrect (e.g., an imputed total unemployment across 10 years of less than 16 months, which we know is not true from even the partial information).

The solution was to calculate self-contained, annual unemployment durations using reports of current and past activities at each individual wave. This was only possible because of the way I had set up the activity histories, and had not been an option with analyses using the 1958 cohort, for which I used a modified form of an existing dataset structured in a way that precluded this. For the 2.3% of participants who skipped waves but later re-entered it was possible to use later reports to fill in employment history gaps retrospectively. This resulted in ten variables of unemployment duration corresponding to each wave which were included in imputation models so that partial employment history information could be utilised and remaining gaps filled in the most valid way. For this reason, it was not possible to simultaneously consider number of unemployment spells in addition to total unemployment duration. Firstly, the inclusion of both would have led to substantial collinearity in the imputation models. Secondly the number of spells could not have been imputed using a strategy of independent annual employment history periods since many spells would continue across several of these periods. The summary variables of total months unemployment and recentness of last unemployment were calculated post-imputation as passive variables.

Summary variables of total months unemployment and recentness of last unemployment were calculated post-imputation as passive variables.

7.3.1.4 Analysis models

Linear regressions using imputed data were used to examine the impact of past unemployment on log-transformed GHQ score in 2011, and logistic regression using imputed data were used to examine the impact of past unemployment on odds of GHQ≥3. Interactions by gender, country, and age group were tested for prior to multiple imputation.

Crude models adjusted for age, sex, and baseline GHQ only, and an 'initial conditions' model additionally adjusted for baseline SEP (RGSC and housing tenure) and health status (self-reported health). Further levels of adjustment explored the addition of SEP, presence of a long-term illness, and current unemployment in 2011 as potential mediating pathways.

Using STATA's svyset command, all analyses took account of clustering by primary sampling unit and strata, and longitudinal weights used to take account of non-random attrition across the 10-year period. Since participants not continuously present between 2001 and 2011 had been assigned longitudinal weights of 0, participants with partial employment history information were effectively excluded from analysis models, but contributed to the imputation process.

7.3.1.5 Sensitivity Analyses

Sensitivity analyses investigated the impact of including health behaviours from both 2001 and 2011, restricting the age range further to participants who had been of working age throughout the entire follow-up period, and of excluding participants taking 'CNS medication' which includes antidepressants.

Table 7.8: Characteristics of initial and final samples (UKHLS)

		Initial sample, present in 2001 and aged 15-64 N=14447 Unimputed data	Initial sample present in 2001 and aged 15-64 N=14447 Imputed data	Final sample, present 2001-2011 N=5,520 Unimputed data	Final sample, present 2001-2011 N=5,514 Imputed data
		(%)	(%)	(%)	(%)
Age at baseline	15-31	32.8	32.8	24.2	24.2
	32-47	36.4	36.4	38.6	38.6
	48-64	30.9	30.9	37.3	37.3
Sex	Male	53.5	53.5	56.9	56.9
	Female	46.5	46.5	43.1	43.1
Country	England	45.1	45.2	48.2	48.2
	Wales	16.1	16.2	15.7	15.7
	Scotland	18.6	18.6	17.2	17.2
	Northern Ireland	20.1	20.1	18.8	18.8
	Missing	0.1	-	0.1	-
SEP at baseline: housing tenure	Owns outright	19.2	19.7	22.8	22.9
	Buying w/ mortgage	53.7	55.0	56.0	56.3
	Council rented	15.9	16.3	13.6	13.6
	Private rented/other	8.8	9.0	7.1	7.1
	Missing	2.4	-	0.4	-
SEP at baseline: occupational social class	Professional	4.3	4.4	5.2	5.3
	Managerial	27.3	28.3	30.4	31.0
	Skilled non-manual	22.8	24.2	24.2	24.9
	Skilled manual	18.1	19.3	16.6	17.2
	Semi-skilled	16.4	17.7	15.3	16.0
	Unskilled	5.6	6.3	5.3	5.7
	Missing	5.6	-	3.1	-
Self-rated health at baseline	Excellent	27.1	27.1	26.9	26.9
	Good	45.2	45.3	46.4	46.5
	Fair	18.7	18.7	19.0	19.0
	Poor	7.1	7.1	6.1	6.1
	Very poor	1.8	1.8	1.6	1.6
	Missing	0.1	-	0.0	-
GHQ at baseline	0-2	67.9	73.0	72.0	73.5
	3+	25.2	27.0	25.9	26.5
	Missing	6.9	-	2.0	
Smoking at baseline	Never smoker	50.5	53.0	54.7	54.8
	Ex-smoker	16.5	17.5	19.6	19.8
	Current, <= 10/day	10.8	11.4	9.2	9.4
	Current, 11-20/day	13.7	14.4	12.8	12.9
	Current, 20+/day	3.5	3.7	3.1	3.1
	Missing	5.0	-	0.5	-
BMI at baseline	18.5-24.9	29.8	42.0	38.7	42.6
	25.0-29.9	24.1	36.7	33.1	36.8
	30.0-34.9	8.6	14.0	11.6	13.3
	>35	3.4	4.5	5.0	5.5
	<18.5	1.2	2.9	1.4	1.8
	Missing	33.0	-	10.3	-
Housing tenure: 2011	Owns outright	17.9	32.0	37.6	37.6
	Buying w/ mortgage	22.4	44.9	43.2	43.3
	Council rented	6.5	14.0	12.1	12.0
	Pvt rented/other	3.9	9.1	7.1	7.1

	Missing	49.4	-	0.1	-
Occupational social class: 2011	Professional	2.7	5.0	5.3	5.3
	Managerial	16.7	32.6	33.5	33.8
	Skilled non-manual	10.9	22.1	22.1	22.5
	Skilled manual	9.3	19.5	18.2	18.5
	Semi-skilled	6.9	14.6	13.8	14.1
	Unskilled	2.7	6.2	5.5	5.7
	Missing	50.9	-	1.7	-
Longterm illness in 2011	Yes	32.0	36.3	36.7	37.6
	No	18.7	63.7	63.3	62.4
	Missing	49.4	-	0.0	
GHQ in 2011	0-2	34.4	75.9	72.1	76.9
	3+	10.2	24.1	21.1	23.1
	Missing	55.5	-	6.9	-
Smoking: 2011	Never smoker	23.0	42.0	44.2	44.2
	Ex-smoker	18.6	34.3	35.3	35.3
	Current, <=10/day	5.1	10.3	9.1	9.1
	Current, 11-20/day	5.4	10.9	9.5	9.5
	Current, >20/day	1.2	2.5	2.0	2.0
	Missing	46.7	-	0.0	-
Drinking frequency: 2011	5+ days/week	6.6	14.2	13.0	14.5
	2-4 days/week	21.1	47.1	41.4	47.2
	Less often	15.1	35.2	29.9	35.3
	Non-drinker	1.2	3.6	2.3	3.0
	Missing	56.0	-	13.4	-
BMI: 2011	18.5-24.9	6.6	25.8	13.8	26.0
	25.0-29.9	9.0	35.3	19.4	36.5
	30.0-34.9	4.9	23.3	10.3	22.1
	>35	2.9	13.1	6.3	13.5
	<18.5	0.2	2.7	0.3	1.8
	Missing	76.4	-	49.9	-
CNS medicine taken	No	18.9	78.0	40.4	78.5
	Yes	4.9	22.0	10.2	21.5
	Missing	76.3	-	49.5	-

Table 7.9: Current and past unemployment in initial and final samples (UKHLS)					
		Initial sample		Final sample	
		Unimputed data	Imputed data	Unimputed data	Imputed data
Employment status 2011	Employed/self-employed	31.0	62.9	60.5	61.2
	Unemployed	1.7	4.2	3.0	2.5
	Sick/Disabled	2.3	5.3	4.4	4.1
	Economically inactive	14.9	27.6	32.0	32.2
	Missing	50.2	-	0.1	-
Total unemployment, 2001-2011	Never unemployed	39.5	78.5	84.3	84.4
	1-6 months	4.1	10.0	7.7	7.7
	7-12 months	1.9	4.3	3.4	3.4
	13-24 months	1.6	3.6	2.9	2.9
	>24 months	1.3	3.6	1.6	1.6
	Missing	51.5	-	0.1	-
Recentness of last unemployment	Never unemployed	39.5	78.5	84.3	84.4
	Current	1.6	4.2	2.5	2.5
	Since 2006	3.3	7.8	6.2	6.2
	2010-2006	4.1	9.5	6.9	6.9
	Missing	51.5	-	0.1	-

Table 7.10: Association of total unemployment 2001-2011 with GHQ score in 2011 (UKHLS) *Reference group is never unemployed in this period*								
	GHQ				GHQ 3+			
Age, sex, country		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.43	-0.00,0.87	0.05	Up to 6 months	1.30	0.97,1.73	0.08
	6-12 months	0.51	-0.20,1.23	0.16	6-12 months	1.68	1.06,2.67	0.03
	13-24 months	1.01	0.24,1.78	0.01	13-24 months	2.13	1.43,3.18	<0.001
	> 24 months	1.04	0.13,1.95	0.02	> 24 months	2.67	1.61,4.42	<0.001
Initial Conditions: Age, sex, country, housing tenure, RGSC, self-rated health, GHQ in 2001		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.35	-0.07,0.77	0.10	Up to 6 months	1.25	0.91,1.72	0.16
	6-12 months	0.37	-0.30,1.04	0.28	6-12 months	1.52	0.94,2.48	0.09
	13-24 months	0.69	-0.06,1.44	0.07	13-24 months	1.70	1.09,2.65	0.02
	> 24 months	0.71	-0.16,1.59	0.11	> 24 months	2.13	1.27,3.60	0.01
SEP pathway: Initial conditions + SEP in 2011		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.35	-0.06,0.75	0.10	Up to 6 months	1.26	0.92,1.73	0.15
	6-12 months	0.33	-0.35,1.00	0.34	6-12 months	1.49	0.90,2.46	0.12
	13-24 months	0.69	-0.06,1.44	0.07	13-24 months	1.69	1.07,2.68	0.02
	> 24 months	0.68	-0.18,1.55	0.12	> 24 months	2.16	1.27,3.65	0.004
Physical health pathway: Initial conditions + physical health in 2011		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.33	-0.09,0.75	0.13	Up to 6 months	1.23	0.88,1.71	0.23
	6-12 months	0.35	-0.30,0.99	0.29	6-12 months	1.52	0.93,2.50	0.09
	13-24 months	0.53	-0.20,1.25	0.16	13-24 months	1.53	0.99,2.36	0.06
	> 24 months	0.63	-0.21,1.48	0.14	> 24 months	2.04	1.21,3.46	0.01
Current unemployment pathway: Initial conditions + current unemployment in 2011		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.36	-0.07,0.78	0.10	Up to 6 months	1.25	0.91,1.73	0.16
	6-12 months	0.39	-0.26,1.05	0.24	6-12 months	1.53	0.92,2.53	0.10
	13-24 months	0.72	-0.09,1.52	0.08	13-24 months	1.70	1.05,2.75	0.03
	> 24 months	0.77	-0.26,1.80	0.14	> 24 months	2.14	1.18,3.89	0.01
Full adjustment: all of the above		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.33	-0.08,0.75	0.11	Up to 6 months	1.24	0.90,1.72	0.19
	6-12 months	0.35	-0.29,1.00	0.28	6-12 months	1.53	0.90,2.59	0.11
	13-24 months	0.58	-0.20,1.36	0.15	13-24 months	1.57	0.97,2.53	0.07
	> 24 months	0.71	-0.28,1.69	0.16	> 24 months	2.16	1.18,3.95	0.01
SA: Initial Conditions plus health behaviours in 2001		Coeff	CI	p		OR	CI	p
	Up to 6 months	0.34	-0.09,0.76	0.12	Up to 6 months	1.24	0.90,1.71	0.19
	6-12 months	0.35	-0.31,1.02	0.30	6-12 months	1.51	0.92,2.47	0.10
	13-24 months	0.67	-0.08,1.42	0.08	13-24 months	1.69	1.08,2.65	0.02
	> 24 months	0.70	-0.17,1.57	0.12	> 24 months	2.11	1.25,3.55	0.01
		Coeff	CI	p		OR	CI	p
SA: Full adjustment + plus health behaviours in 2001 and in 2011	Up to 6 months	0.34	-0.07,0.74	0.10	Up to 6 months	1.24	0.90,1.72	0.19
	6-12 months	0.34	-0.30,0.98	0.29	6-12 months	1.52	0.89,2.57	0.12
	13-24 months	0.62	-0.17,1.40	0.12	13-24 months	1.61	0.98,2.64	0.06
	> 24 months	0.74	-0.25,1.72	0.14	> 24 months	2.14	1.16,3.97	0.02

Table 7.11: Association of recentness of last unemployment 2001-2011 with GHQ score in 2011 (UKHLS) *Reference group is never unemployed in this period and not currently sick/disabled in 2011*								
Adjustment Level	GHQ				GHQ 3+			
Age, sex, country		Coeff	CI	p		OR	CI	p
	Current	0.90	0.12,1.68	0.02	Current	2.36	1.43,3.89	<0.001
	2006-2011	0.39	-0.08,0.86	0.11	2006-2011	1.52	1.11,2.09	0.01
	2001-2006	0.41	0.01,0.82	0.05	2001-2006	1.39	1.01,1.92	0.05
Initial Conditions: Age, sex, country, housing tenure, RGSC, self-rated health, GHQ in 2001		Coeff	CI	p		OR	CI	p
	Current	0.64	-0.15,1.43	0.11	Current	1.86	1.10,3.17	0.02
	2006-2011	0.29	-0.14,0.72	0.18	2006-2011	1.45	1.05,1.99	0.02
	2001-2006	0.31	-0.08,0.70	0.12	2001-2006	1.29	0.91,1.83	0.16
SEP pathway: Initial conditions + SEP in 2011		Coeff	CI	p		OR	CI	p
	Current	0.65	-0.15,1.45	0.11	Current	1.89	1.09,3.27	0.02
	2006-2011	0.30	-0.14,0.73	0.18	2006-2011	1.46	1.05,2.02	0.02
	2001-2006	0.33	-0.06,0.72	0.10	2001-2006	1.32	0.92,1.88	0.13
Physical health pathway: Initial conditions + physical health in 2011		Coeff	CI	p		OR	CI	p
	Current	0.51	-0.28,1.31	0.20	Current	1.69	0.97,2.93	0.06
	2006-2011	0.27	-0.16,0.70	0.22	2006-2011	1.43	1.04,1.97	0.03
	2001-2006	0.29	-0.10,0.67	0.14	2001-2006	1.27	0.88,1.81	0.20
Full adjustment: all of the above		Coeff	CI	p		OR	CI	p
	Current	0.54	-0.27,1.34	0.19	Current	1.72	0.98,3.04	0.06
	2006-2011	0.28	-0.15,0.71	0.21	2006-2011	1.45	1.04,2.01	0.03
	2001-2006	0.31	-0.08,0.70	0.12	2001-2006	1.30	0.90,1.86	0.16
SA: Initial Conditions plus health behaviours in 2001		Coeff	CI	p		OR	CI	p
	Current	0.64	-0.15,1.44	0.11	Current	1.89	1.11,3.19	0.02
	2006-2011	0.28	-0.15,0.71	0.20	2006-2011	1.43	1.04,1.97	0.03
	2001-2006	0.30	-0.09,0.69	0.13	2001-2006	1.27	0.89,1.81	0.18
SA: Full adjustment plus health behaviours in 2001 and in 2011		Coeff	CI	p		OR	CI	p
	Current	0.56	-0.25,1.36	0.17	Current	1.75	0.99,3.09	0.06
	2006-2011	0.29	-0.13,0.72	0.17	2006-2011	1.45	1.04,2.02	0.03
	2001-2006	0.31	-0.07,0.70	0.11	2001-2006	1.29	0.90,1.85	0.17

7.3.2 Results

Differences in initial v. final samples:

The initial and final samples differed with respect to most characteristics (Tables 7.8, 7.9). A comparison of participants excluded and participants retained in analytic models using imputed data showed that retained participants were significantly older, more likely to be female, and from England. They smoked less and had lower BMI at both time-points. They were more likely to be homeowners at both time-points, and of more advantaged occupational social class at both time-points. They had less past unemployment, and were less likely to be currently unemployed than excluded participants (all p<=0.001).

7.3.2.1 Total unemployment in months, 2001-2011

Crude models and models adjusting for initial conditions showed an approximately stepwise pattern to the association of total unemployment over the study period with both total GHQ and odds of above-cutoff GHQ. Attenuation of effect sizes between crude and initial conditions models supports the operation of direct and indirect selection in this relationship (Table 7.10). At this stage, associations with total GHQ ceased to be significant although substantial effect sizes remained.

In mediation models, the addition of SEP and current unemployment in 2011 barely altered effect sizes. Adjusting for long-term illness in 2011 did produce some attenuation for total GHQ effects, especially for the top groups (13-24 months and >24 months of unemployment). In models adjusting for SEP, current unemployment and long-term illness simultaneously, apparently stepwise associations remained with above-cutoff GHQ score. However, despite substantial effect sizes, associations for the most part failed to reach significance, suggesting this analysis is hampered by lack of power due to small exposure groups or overall sample size.

Most recent unemployment, 2011

A comparison of age, sex, and country-adjusted models with those adjusting for initial conditions again supported the operation of direct and indirect selection by prior mental health and SEP. Again, mediation models suggest little influence of SEP at outcome, but an influence of long-term illness. Throughout successive levels of adjustment, associations of current unemployment were stronger than past unemployment, with an apparent stepwise effect of recentness visible for associations with dichotomized GHQ and (Table 7.11). While effect sizes were substantial even with full adjustment, associations for the most part failed to reach significance, indicating inadequate power.

Results of sensitivity analyses

Effect sizes were not substantially altered with addition of smoking and BMI in 2001 to initial conditions models (Tables 7.10, 7.11), nor with addition of health behaviours in 2001 and 2011 to

the fully-adjusted models, indicating that these factors do not substantially confound or mediate associations between unemployment and depressive symptoms in this population. Further sensitivity analyses performed as variations on the initial conditions model indicated that exclusion of participants taking CNS medication did not much alter effect sizes, although confidence intervals widened due to further restriction of the sample size.

Restricting the age range further to people who had been of working age throughout the whole 10-year period did not substantially change effect sizes for total unemployment but did appear to strengthen associations in analyses of recentness. Adjusted for initial conditions, elevation in GHQ was 0.54 (p=0.05) for last unemployment in 2006-2011 and 0.45 (p=0.04) for last unemployment in 2001-2006; corresponding odds ratios for GHQ 3+ were 1.58 (p=0.01) and 1.35 (p=0.08).

Interactions by gender, country, and age group had been tested for in the unimputed data and were not supported, so they were not taken further.

7.4 Discussion

7.4.1 1958 Cohort Study

After adjusting for sex, SEP, mental health, and physical health at labour market entry, significant and often substantial associations with total MI score at 50 were seen for participants with who had experienced more than one year of unemployment, and participants who had experienced 1, 2, or 3 spells, compared to participants never unemployed. These associations appeared roughly stepwise even where not all groups were significant, supporting an accumulation model.

First unemployment when aged 16-21 was more strongly associated with later MI score than first unemployment later in life, but additional analyses suggested this was confounded by total unemployment rather than indicating either a sensitive period effect or confounding by education.

With the exception of recentness of last unemployment, SEP at 50 appears to substantially explain many of these effects, suggesting the operation of an indirect pathway between past unemployment

and psychological health at age 50 via reduced social mobility and/or downward social mobility. The smaller attenuations observed with adjustment for current unemployment suggest the effects of past unemployment on mental health may also partly operate by increasing the likelihood of unemployment in the future. Physical health at 50 did not appear to explain much of the associations.

As discussed previously, it was possible that to the extent that smoking, drinking, and BMI could causally influence depression, health behaviours might mediate associations between unemployment and depression if unemployment also had an effect on these factors. In addition, it was possible that to the extent that these factors could influence unemployment and depression independently, they could act as confounders producing spurious associations between those two. At the same time, concerns that including health behaviours would be overadjustment (as discussed in chapter 1) led to the decision to include these factors in sensitivity analyses only. In any case, the effect of including the block of health behaviours across the models proved to be modest. This supports the view that these factors are unlikely to substantially influence depressive symptoms, and hence unlikely to meaningfully confound or mediate any impact on depressive symptoms of unemployment.

Consistent with the extensive evidence for cross-sectional associations between unemployment and depression, associations with both total MI score and odds of MI 4+ were robust and very strong for participants currently unemployed. However, these results do not support the existence of substantial, lasting, and direct effects on mental health of unemployment which has ended. Since effects for unemployment which had ended were mostly explained by SEP, this suggests any effects of unemployment on psychological health not mediated through either SEP or later unemployment are largely transitory.

Across analyses, associations with log-transformed MI score were more robust than associations with odds of clinically relevant symptoms, which tended to approach the null in later models except for the currently unemployed. While this may reflect a statistical issue, that analyses of continuous outcomes are more often significant, it also suggests that any remaining effects of unemployment on psychological health following re-employment, though detectable, are not of the magnitude to increase likelihood of clinically relevant symptoms.

7.4.1.1 Limitations

As discussed with reference to analyses of inflammatory markers at age 45 using this dataset, the first limitation concerns the quality of the data. While the updated version of the AHD provides a more accurate account of participants' activity histories in the years prior to outcome measurement, substantial errors are likely to remain in the histories, leading to misclassification of exposure. A second, related concern is that for this relationship in particular, a degree of reporting bias cannot be ruled out, since depressed people may be more likely to recall negative events.

Thirdly, exclusion of participants was non-random in a way which would be expected to lead to underestimation of effects. Fourthly, information was not available on whether participants at sweep 8 were taking antidepressants, the likely impact of which is unclear. To the extent that antidepressant use may have lessened MI score among participants who had experienced unemployment, this may have produced underestimation of effects. On the other hand, if participants who had experienced unemployment were for some reason less likely to be prescribed antidepressants, effects could have been inflated. Finally, the fact that all participants in the sample are the same age means it was not possible to definitely separate recentness of unemployment from the age at which it occurred.

7.4.2 UKHLS

This analysis found substantial associations of depressive symptoms as measured by GHQ with past unemployment (both total aggregated unemployment and spells ending in the past 5 years or 5-10 years ago) after accounting for initial conditions, although in this fairly small sample associations did not always reach significance. While mediation models suggested that, in this population, any effects are explained more by physical or overall health than by SEP, it should be noted that some of the participants with a long-term illness in 2011 will have been experiencing depression, producing overadjustment in those cases. In any case, conclusions cannot be easily drawn as to the exact nature of any scarring mechanisms, since the sample is clearly underpowered and the estimates imprecise.

7.4.2.1 Limitations

As noted, it was not possible to determine whether cases of long-term illness included depression, leading to overadjustment in some cases. A strength of this analysis is that the annual collection of data in this survey should have minimised recall error and hence misclassification of exposure, while the use of longitudinal weights should have minimised the impact of non-random attrition over the 10-year period. Nevertheless, a major limitation concerns the small number of participants continuously present over the 10-year period, with the result that this analysis appears underpowered.

7.4.3 Support for hypotheses

These results support the hypotheses that depressive symptoms increase with increasing aggregated unemployment, and that the association is stronger for more recent spells. However, no evidence was found for the hypothesised sensitive period effect of youth unemployment.

7.4.4 Fit with previous research

In their support for strong associations of depressive symptoms with current unemployment and additional associations with past unemployment, both sets of analyses accord with the considerable evidence of cross-sectional associations between unemployment and impaired mental health, and with the much smaller literature reporting scarring effects of unemployment on mental health.

Analyses of aggregated unemployment in the NCDS, despite a number of methodological differences and use of updated activity history information, reached similar conclusions to the recent analysis by Daly & Delaney in this dataset[118]. This also used NCDS data to examine effects of total unemployment in years since 16 on Malaise Inventory at age 50, but some key differences meant that my analysis extended that work in several ways. Firstly, a newly updated and more accurate version of the Activity Histories Dataset was used which took into account reports of current activity from the biomedical sweep. Secondly, the choice of covariates is somewhat different, reflecting a different conceptual model. Thirdly, my analysis operationalised lifetime unemployment in three additional ways besides total aggregated unemployment, and in each case explored associations with odds of clinically relevant symptoms in addition to continuous MI score.

In their support for accumulation effects, the results of both NCDS and UKHLS analyses accord with the psychological scarring effects of unemployment in the Northern Swedish Cohort reported by Strandh, where an accumulation effect on psychological distress at 42 was seen with number of periods (ages 16-21, 21-30 and 30-42) in which participants experienced unemployment[20]. However, Strandh also argues for an independent sensitive period effect, due to the predictive association of discrete periods of unemployment between the ages of 16-21 and 21-30 but not 30-42. The difference may result from how unemployment was measured; my analyses included a more detailed measure of total unemployment in months across aggregated periods, whereas in Strandh's analysis period-specific unemployment was coded to 1 if 6 months or longer and 0 otherwise, such that total unemployment could only take values of 0, 1, 2, or 3. The comparative explanatory power

could well be explained by a relative loss of detail in the accumulation measure. Alternatively, if younger jobseekers are more psychologically vulnerable to non-financial aspects of unemployment due to not yet having established an occupational identity[2], we might expect more of a sensitive period effect in a country where more extensive unemployment protection means that non-financial aspects play a comparatively greater role in how unemployment impacts people's lives.

The weak evidence for a lasting effect of discrete periods of recent but ended unemployment is in contrast to work by Lucas[284] reporting that a person's set-point for life-satisfaction appears altered by a period of unemployment several years after re-employment, suggesting that life-satisfaction and depressive symptoms may be affected differently by socially adverse events.

The importance in mediation models of SEP is consistent with the economic literature on scarring effects of unemployment which show long-term impacts on not just wages but job quality and security [18, 282, 283].

7.5 Chapter Summary

In both sets of analyses, total aggregated unemployment was robustly associated with depressive symptoms, especially for participants who had experienced the most unemployment. In NCDS analyses this appeared largely mediated by SEP whereas in UKHLS presence of a long-term illness explained a greater degree of associations. Both sets of analyses found further evidence supporting the strong cross-sectional associations of unemployment and depressive symptoms previously reported, as well as smaller effects for discrete periods of recent unemployment which had ended. No evidence was found for sensitive period effects after taking into account total unemployment.

8 OVERALL DISCUSSION

8.1 Chapter overview

This chapter will summarise the results of chapters 4-7 and discuss them with reference to the aims, objectives and conceptual framework set out at the start of this thesis. I will identify overarching issues, and suggest future avenues for research and discuss policy implications.

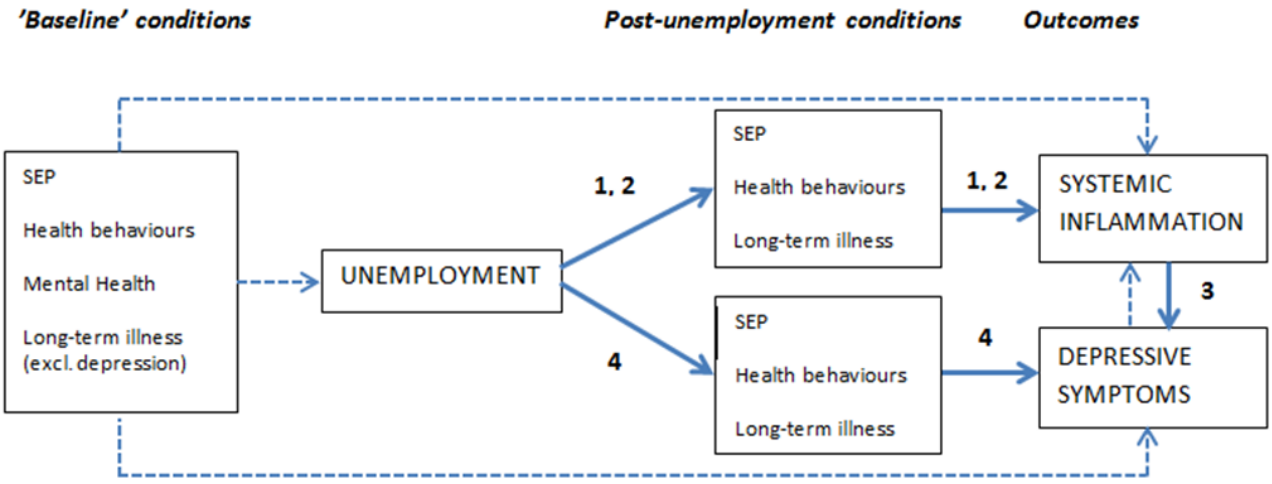
8.2 Summary of Findings

8.2.1 Aim, objectives, and conceptual framework:

The aim of this PhD was to use longitudinal and cross-sectional data to examine associations between unemployment, inflammation, and depressive symptoms in UK participants of working age. The specific objectives were as follows:

1. To examine cross-sectional associations between current unemployment and inflammation.
2. To examine associations of inflammatory markers at outcome with aggregated unemployment and number of spells during follow-up, time since an unemployment spell, and life period in which first unemployment occurred.
3. To examine the direction of association between inflammation and depressive symptoms.
4. To examine associations of depressive symptoms with aggregated unemployment and number of spells during follow-up, time since an unemployment spell, and life period in which first unemployment occurred.

Figure 8.1: Conceptual framework based on previous literature



8.2.2 Objective 1

Meta-analytic models found an overall cross-sectional association of current unemployment and systemic inflammation as indexed by CRP and fibrinogen across all available study populations. Since this was robust to adjustment for socioeconomic position, long-term illness, and symptoms of depression/anxiety, this does not appear to be the result of either indirect selection (i.e., selection into unemployment on the basis of disadvantaged social position) or direct selection (i.e., selection into unemployment on the basis of poor health). Since this was also robust to adjustment for smoking, drinking, and BMI, it does not appear to result from confounding by these factors, nor to be substantially mediated by them. Country within the UK emerged as an important effect modifier, with stronger effects in Scotland than England and even stronger effects in Wales, although the small sample size for that country even in the pooled analysis mean estimates are imprecise. No effect modifications by gender or age were seen in the pooled analyses. However, substantial variation between the studies (with no robust associations in UKHLS data) remain unexplained and suggest that additional sources of heterogeneity may affect this relationship.

8.2.3 Objective 2

In contrast to cross-sectional associations with unemployment, little evidence was found for effects of total aggregated unemployment on systemic inflammation. An association with fibrinogen specifically was seen for participants who had experienced the most unemployment – although the small sample sizes in UKHLS analyses meant associations in that dataset did not reach significance – suggesting an independent pathway affecting fibrinogen may be operating. No associations were seen between the number of spells experienced and either CRP or fibrinogen, suggesting that any non-inflammatory pathway affecting fibrinogen is affected more by the total time spent unemployment than the number of events. No evidence was found in either study population for an impact on inflammatory markers of recent but ended unemployment, suggesting that any effects of unemployment on this particular aspect of health are not long-lasting. No association was seen in the NCDS between markers of inflammation and the age at which unemployment first occurred, against the hypothesis that unemployment at certain ages may set people on trajectories leading to elevated inflammation later in life. In combination with results of cross-sectional analyses, this suggests that any inflammatory effects of unemployment can under certain conditions be substantial but are largely transitory, although scarring effects impacting fibrinogen may operate through an additional pathway linked to accumulation rather than sensitive period effects.

8.2.4 Objective 3

No robust predictive associations were found for CRP and later depressive symptoms in either dataset, although NCDS analyses did find an association of fibrinogen and later depressive symptoms specifically. Analyses do not therefore support a causal role of systemic inflammation itself in depressive symptomatology, although an independent pathway involving fibrinogen but not CRP may be implicated. In NCDS analyses, substantial attenuation of effects with addition of health behaviours to CRP and fibrinogen models indicated a potentially important role for these factors but whose exact nature is unclear. They may indicate that to some extent adverse health behaviours,

inflammation, and later depressive symptoms are all on a common causal pathway such that health behaviours have some influence on depressive symptoms via inflammation. However, since even in models not adjusting for health behaviours CRP did not significantly predict Malaise Inventory, this interpretation of the role of health behaviours in this population does not affect the overall conclusion - that a causal role of inflammation in depression is not supported by this thesis.

8.2.5 Objective 4

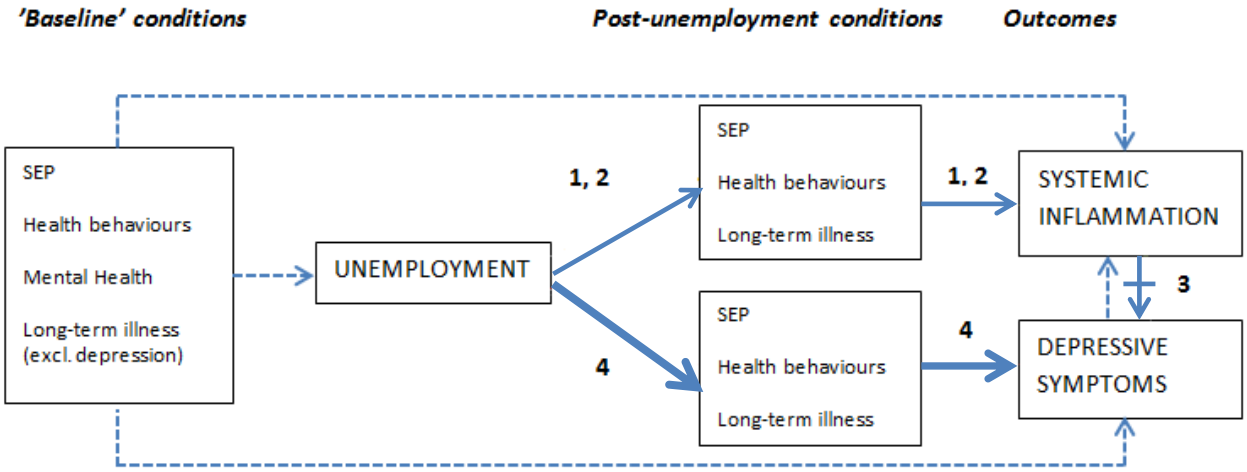
Consistently across both study populations, past unemployment – measured as total months unemployed, number of spells or presence of discrete periods of recent but ended unemployment – was associated with elevations in depressive symptoms after adjustment for confounders, although the low power of UKHLS analyses affected significance. Alongside very strong associations of current unemployment and depressive symptoms, these longitudinal associations support previous evidence of 'scarring effects' of unemployment on later mental health, with mediation models pointing to SEP as an especially important pathway. These results are therefore consistent with the evidence discussed in the literature review that unemployment can have long-lasting effects on wages and social position more generally even following re-employment. Importantly, mediation by later SEP was independent of pre-unemployment SEP, indicating that the 'indirect selection' by prior social position known to occur in studies of unemployment and health cannot account for this. Models did not support an independent sensitive period effect for youth unemployment when total unemployment was taken into account.

8.2.6 Revised conceptual framework

To summarize these findings, a modified form of the original conceptual framework is shown below. Arrows representing partially supported pathways are shown as standard-weight solid arrows (the pathway from unemployment to inflammation, since only a cross-sectional association is supported but not a longitudinal one). Fully supported pathways are presented in bold (from unemployment to depressive symptoms via mediating factors), and pathways not supported by results are presented

with a horizontal line through the arrow (the pathway from systemic inflammation to depressive symptoms). As in the original framework the narrow dotted lines represent confounding or reverse-causation pathways with respect to hypotheses, whose operation were supported by patterns of attenuation visible in the results of this thesis.

Figure 8.2: Conceptual framework, revised post-analysis



8.3 Emergent Themes

8.3.1 Lifecourse influences

In longitudinal models of unemployment and later depressive symptoms, CRP and fibrinogen, substantial attenuation occurred with adjustment for occupational social class and housing tenure at baseline (age 16 for all participants in NCDS analyses, a mix of ages and 10 years prior to outcome measurement in UKHLS analyses). Especially in the case of NCDS analyses where this corresponds to labour market entry, this underscores the importance of early socioeconomic factors in predicting both health outcomes and experience of social adversity. Meanwhile in longitudinal models of inflammation and depression in NCDS, an unexpected attenuation with adjustment for earlier health behaviours suggests that unobserved heterogeneity in early life factors independent of parental social class may have been affecting CRP, depressive symptoms, and health-related behaviours

independently. If this interpretation of the results is correct, it would again underscore the influence of early-life factors on associations between diverse health outcomes many years later, and the importance of considering such influence when studying associations between health and social factors later in life.

8.3.2 Discrepancy between CRP and fibrinogen

In chapter 5 and chapter 6 CRP and fibrinogen were both used as markers of systemic inflammation, since both are acute phase proteins whose concentrations increase greatly in the final stages of the inflammatory cascade. However a common and unexpected finding was the visible association (of depression and unemployment, respectively) with fibrinogen in the absence of a corresponding association with CRP.

In both cases, this calls into question the hypothesised relationship with systemic inflammation but leaves open the possibility of an association with fibrinogen specifically resulting from a non-inflammatory process. Since the two relationships explored in these chapters are so different, it cannot be assumed that the same non-inflammatory mechanism is responsible. That the exclusion of participants taking potentially anti-inflammatory medications did not make the strength of associations with CRP and fibrinogen converge suggests the discrepancy cannot be explained by a differential effect of these medications on the two molecules.

It is, however, possible that the repeated discrepancy between CRP and fibrinogen reflects residual confounding by a health behaviour or social factor which affects fibrinogen more than CRP. This could be either an early-life exposure or something reflecting current circumstances such as recent occupational-related injuries, which would be expected to elevate fibrinogen and also expect to be socially patterned. Alternatively, and especially relevant to unemployment analyses, area-level confounding could be involved if fibrinogen is affected by a local factor such as certain kinds of pollution, which could vary on a geographically small scale and be higher in parts of the UK where

unemployment is concentrated. While testing these hypotheses is clearly beyond the scope of this thesis, they are something which future research could seek to explore.

8.3.3 Heterogeneity in associations of unemployment and health

Another theme emerging from this thesis is the substantial heterogeneity in associations of unemployment and health outcomes. This was visible firstly in cross-sectional meta-analysis of unemployment and inflammation, in which strong country effects were apparent, and substantial study effects were also seen. But it was also visible in the discrepancy between the results of longitudinal analyses of unemployment, with a complete lack of evidence for scarring effects of unemployment on inflammation which contrasts sharply with robust associations with later depressive symptoms. This overall pattern is therefore consistent with previous research into unemployment and health showing that the strength and direction of associations differs markedly according to both the health outcome in question and an array of modifying factors, many of which merit further investigation.

8.4 Limitations of the current research

8.4.1 Inadequate power

The main limitation of the longitudinal analyses using the BHPS component of UKHLS was the lack of power, resulting from a combination of high attrition rates and, for CRP and fibrinogen analyses, a low response rate for blood samples. The result was highly imprecise estimates for longitudinal analyses of unemployment, despite a high degree of accuracy in measurement of exposure.

8.4.2 Gender Issues

Furthermore, the comparatively small number of unemployed participants in the study populations used meant that it was not feasible in power terms to stratify all unemployment-related analyses by gender. As previously discussed, a tendency of women jobseekers to describe themselves as looking after family could produce gender-specific exposure misclassification in mixed-gender studies of

unemployment and health. Thus, while previous studies restricted to male workers have the limitation of not being generalizable beyond one gender, they may have the advantage of more accurately capturing associations for that gender. While the decision to include women means the analyses in this thesis avoided the first problem, it is possible that to some extent they fall foul of the latter. Furthermore, while it does not seem likely that there are substantive gender differences in the effects of psychosocial stressors on inflammatory pathways, social influences systemic inflammation may be harder to detect in women due to comparatively greater 'noise' linked to the menstrual cycle. Again, this could have produced comparatively greater measurement error for female participants; both these reasons there would ideally have been sufficient unemployed women in the samples to facilitate adequately powered, gender-stratified analyses. Suggesting that these problems did not substantially affect results is the fact that interaction terms for gender were checked for throughout and found in all cases to be non-significant. However, it is possible that due to small numbers of unemployed participants and especially unemployed women, gender differences in associations of unemployment were present but not detectable by interaction tests.

8.4.3 Data Inaccuracies

Conversely, in longitudinal NCDS analyses a much better sample size may have been offset by inaccuracies in the measurement of past unemployment. The extent of the mismatch between the two accounts of employment status at the biomedical sweep indicates these inaccuracies may be substantial.

8.4.4 Discontinuities and measurement error in mental health measures

It was not ideal that in the NCDS measurement of mental health changed several times between sweeps, since the different scales used (the Rutter Questionnaire at age 16, Malaise Inventory at 23, 33, 42, and 50, and the CIS-R at 45) aim to capture related but distinct underlying constructs. This firstly affected longitudinal models of the impact of unemployment on depressive symptoms, where it was not possible to adjust for the same measure of depressive symptoms at baseline as at outcome. It also meant that in the investigation of whether inflammatory markers predict later depressive symptoms, the only way to adjust for baseline value of the outcome using an equivalent measure was by adjusting for a proxy measure of baseline mental health taken two years prior to baseline.

Meanwhile, in analyses of the inflammation-depression association in Chapter 5, using the average of Malaise Inventory at age 33 and 42 for a baseline measure of depressive symptoms led to greater attenuation of effect sizes than using a simpler, more recent measure of Malaise Inventory at 42. This suggests MI is a rather labile measure, and hence that any given measurement of MI symptoms may be substantially affected by measurement error due to random short-term variation, to the extent that incorporating measurements from almost a decade before baseline improved the measurement of typical MI symptoms many years later. More generally, this served as a reminder of the limitations of depressive symptoms as measured in large-scale epidemiological surveys, for which random variation may have a tendency to obscure more deterministic patterns.

8.4.5 Weights

A further limitation was that, due to a lack of appropriate weights, it was not possible to weight NCDS and HSE/SHeS analyses. To the extent that non-response was non-random, this may have led to bias in those analyses.

8.5 Future Research

The country modification in cross-sectional associations of unemployment and inflammatory markers was unexpected, and suggests several further avenues for research which could further shed light on what is driving this effect. Firstly, the very strong effects which emerged in the meta-analysis for the Welsh subsamples were nevertheless imprecise owing to restricted sample sizes. These results therefore point to a need for more research into associations of unemployment and biomarkers on a larger scale in that country specifically if and when appropriate data becomes available. In the meantime, a natural avenue to explore would be associations in Wales of unemployment with aspects of health known to be related to inflammation, such as cardiac health, for which data is currently available.

Insofar as background unemployment rate is implicated as an important modifying factor, a natural extension of this research would involve an investigation of associations of unemployment and inflammation using smaller-scale geographical units, closely informed by local-level labour market statistics. With the UK data currently available this would simply not be possible; but it could perhaps be done with further aggregation of data sources, for instance European or US data. An additional reason to investigate this relationship using smaller-scale geographical areas is that doing so could shed some light on environmental processes either mediating or confounding longitudinal associations with unemployment and fibrinogen, and potentially explain the discrepancy between results for fibrinogen and CRP.

Aspects of this research could also be extended by incorporating a qualitative aspect. In the survey data used for these analyses it was not possible to test the hypothesis that country/regional modifications observed in cross-sectional data are ultimately explained by the impact of background unemployment rate on jobseekers' expectations of re-employment. For such a question, qualitative interview techniques would likely be more appropriate.

Looking further afield, since even the cross-sectional relationship of unemployment and inflammation has been very little studied, a further aggregation or meta-analysis including European surveys would extend the research to date on this relationship beyond the UK, US, and Finland. This would allow modifying effects of welfare state regime – known to be substantial for other aspects of health – to be systematically explored. Thinking temporally rather than geographically, one possible extension to both the longitudinal and cross-sectional aspects of this thesis concerns the historical period in which data was collected. This thesis drew on data spanning from 1998 to 2011, with outcomes for the most part measured in 2003, 2008 or 2011. While stratified meta-analyses indicated that temporal period defined as pre- or post-crash did not account for much heterogeneity in cross-sectional associations of unemployment and inflammatory markers, one potential modifier which it was not possible to examine was the impact of policy changes surrounding unemployment and welfare more generally enacted following the 2010 election. It is unclear how these changes, which have profoundly changed the experience of unemployment, will have affected relationships of unemployment with health. The threat of benefit sanctions for missed appointments or so-called 'workfare', i.e., being required to work close to full-time hours unpaid in order to receive jobseekers' allowance, will have provided extra impetus for jobseekers to accept work more quickly, and in doing so may have affected the selection mechanisms acting on jobseekers. At the same time, these changes may well have made unemployment a more distressing experience while it lasts and exacerbated its causal impact on both mental and physical health. Given the evidence from economic literature that less generous unemployment protection reduces employment durations but exacerbates scarring effects of unemployment by forcing jobseekers in lower paid work sooner, these changes may also have had an effect on longitudinal associations with past unemployment. Alongside these developments, the nature of employment has also been changing with the increase in zero-hour contracts and self-employment. The likely net effect of these mechanisms is unclear, and as data collected very recently becomes available an extension of this research would be to investigate this.

For the longitudinal analyses of unemployment and depressive symptoms, a natural extension to mediation analysis would be to further investigate the intervening influence of SEP, longterm illness, health behaviours, later current unemployment, and health behaviours using structural equation modelling or path analysis. A more sophisticated approach to mediation analysis, this would allow the contribution of these intervening factors to be investigated simultaneously, accounting for one another. This could also be applied to cross-sectional analyses of unemployment and inflammation, although cross-sectional mediation analysis is harder to interpret in terms of causal mechanisms.

Lastly, the exact role of health behaviours in associations between systemic inflammation and depressive symptoms in the NCDS remains unclear, but may point either to life-course influences confounding relationships in midlife or a change in the impact of health behaviours on inflammation around the age studied. While in any case these models did not support a causal role of systemic inflammation in depression, research aiming to further unpick the independent influence of health behaviours on both systemic inflammation and depression in this dataset, and how health behaviours impact inflammation at different ages in other datasets, would be warranted.

8.6 Policy Implications

The lack of evidence found in this thesis for a causal role of systemic inflammation in depressive symptomatology suggests one of two explanations: either that no such causal relationship exists, or the associations seen under lab conditions and in some previous epidemiological studies reflect a causal role which is sufficiently minor at the population level as to be often swamped by other influences. In either case, these results suggest that directly targeting social factors linked to depression – for example, unemployment, which this thesis showed was predictive of depressive symptoms both concurrently and years later – may have a greater impact on this aspect of health. While these analyses did not find evidence of long-term scarring effects of unemployment on markers of systemic inflammation, overall cross-sectional associations of unemployment and CRP and fibrinogen support the view that inflammation may be in the short-term causally involved in

processes linking unemployment to chronic disease, at least under certain conditions. Since the geographical patterning of associations goes against a model on which the poor health of jobseekers can be largely explained by health-related selection into unemployment, these results have implications for a broader debate about the extent to which unemployment impacts health as opposed to vice versa, and hence how economic policy affecting unemployment rates may impact on health.

8.7 In retrospect

In retrospect, certain decisions could have been made differently with regard to the overall structure of this thesis, in which the longitudinal analyses of unemployment (Chapter 5 and 7) were conducted first using NCDS and then replicated within the BHPS component of Understanding Society. While replication can be illuminating, this may not have been an ideal use of time given both the number of months required to construct the BHPS employment histories dataset and power issues limiting interpretation of the BHPS results. On the other hand, it eventually became clear that longitudinal analyses of unemployment and depressive symptoms using the NCDS in Chapter 7 could have been usefully extended with structural equation modelling to further explore the direct and indirect pathways accounting for those associations. If starting again, I would therefore use UKHLS data only for Chapter 6, but extend the NCDS component of Chapter 7 considerably by applying SEM techniques.

8.8 Conclusion

This thesis set out to investigate associations between unemployment systemic inflammation as a possible explanation for elevated morbidity and mortality among jobseekers. Its results supported a cross-sectional association of current unemployment and inflammation, but one which appears highly variable according to context and between populations. In contrast, a longitudinal impact of past unemployment on systemic inflammation was not supported, indicating that any effects of

unemployment on this aspect of health are largely transitory. This thesis also set out to investigate the longitudinal influence of past unemployment on symptoms of depression, and found evidence for scarring effects in which socioeconomic position is an important mediator, and accumulation processes better supported than a sensitive period effect. Meanwhile, no evidence was found for a causal influence of systemic inflammation in depressive symptomatology, suggesting that any such impact, if it exists, is not large enough to be visible beyond experimental settings, in real-world measurements at the population level taken months or years apart. Taken together with the robust associations of aggregated unemployment and later depressive symptoms, results therefore underscore the preventative potential of modifications to social determinants of mental health, as opposed to medicinal attempts to intervene in molecular processes linked to depression.

9 APPENDICES

9.1 APPENDICES RELATING TO CHAPTER 1: LITERATURE REVIEW

9.1.1 Appendix A: Summary of longitudinal studies investigating inflammation to depression

Authors and year	Inflammatory markers used	Depression measure	Follow-up	Analysis type	Population	N	Covariates	Result	This direction supported?	Limitations
Glaser 2003 [234]	IL-6 (pre-treatment)	Beck Depression Inventory-Short Form (BDI-SF)	14 days	Repeated-measures linear regression	Older adults (43 men, 76 women) aged 48-89 (mean age 71.2) undergoing influenza vaccination	119	Baseline BDI-SF, caregiver status, ethnicity, education, weight, alcohol intake, plus cardiac medication and B-blockers in additional models Sex, age, smoking, exercise, vaccine history were not included since they were not associated with IL-6 or BDI score Other medications were not included since their use did not appear related to IL-6	Depressive symptoms during follow-up did not change significantly, and were not related to baseline IL-6 levels	No	
Van den Bigelaar 2007 [240]	CRP, IL-6, IL-1β, TNF-α, IL-1ra, IL-10	The 15-item Geriatric Depression Scale (GDS-	Annual data collection for 5 years	Mixed linear models, accounting for	Men (37%) and women (63%) aged 85 at baseline.	267	Gender, education, cognitive impairment (MMSE score at different time	Baseline CRP predicted accelerated increase in	Yes for CRP, and possibly for IL-1β.	Participants were aged 85-90. The authors stress

		15). A score of 5 was used as a cut-off for incident depression		correlations between repeat measurements	Participants were ineligible if at baseline they showed depressive symptoms (GDS ≤2), cognitive decline (MMSE≥24) or were taking corticosteroid medication		points), comorbidity (history of stroke/ chronic disease, subjective well-being, disability in daily functioning, current smoking, BMI, serum albumin levels)	depressive symptoms ($p<0.001$) A similar trend was found for IL-1β ($p=0.06$) An inverse association with development of depression was found for IL-1ra ($p=0.003$)	Implications re: IL-1ra are less clear. The authors interpret its apparent protective effect as consistent with a causal role for inflammation in depression, since IL-1ra is an *antagonist* to a pro-inflammatory cytokine. This is directly against the interpretation of Milaneschi's results (below)	that their findings cannot be extrapolated to depression in young and middle age, whose aetiology may well be different
Rohleder 2008 [60]	IL-6 and CRP	10-item version of the CES-D	20 weeks	hierarchical linear regression	Young women, mean age 18.6 (SD: 1.4, range: 16.1–20.9)	65	Age, BMI, baseline IL-6/CRP	No predictive effects of baseline IL-6 or CRP were found	No	
Gimeno et	IL-6 and CRP	A four-item	11.8 years	Path analysis	British civil	3339 to	Baseline cognitive	Baseline CRP and	Yes for	'The cognitive

al 2008 [235]		sub-scale of the General Health Questionnaire measuring cognitive symptoms of depression only	(mean)		servants. Mean age 50, 30% female	3370	symptoms of depression, sex, SEP (employment grade), ethnicity, alcohol intake, diet, physical activity, smoking, blood pressure, BMI, waist:hip ratio, total:HDL cholesterol ratio, CHD, type 2 diabetes, respiratory illness, medications (CHD, diabetes and central nervous system medication, anti-depressants, analgesics, female sex hormones).	IL-6 both robustly predicted cognitive symptoms of depression at follow-up (CRP: p=0.04, IL-6: p=0.02) in adjusted models Effects were slightly stronger in men, but no statistical evidence of an interaction	cognitive symptoms of depression.	symptoms of depression can be considered an indicator of early stages of clinically diagnosed depression. Thus, our results suggest that inflammation plays a role as an initiator and contributor to the progression of depression, rather than contributing to its later development.'
Stewart et al 2009 [239]	IL-6 and CRP	Beck Depression Inventory (BDI-II). Cognitive-affective and somatic-vegetative subscales were also examined	6 years		Mean age 61.0, 51.7% female	263	Baseline BDI-II score. Baseline age, gender, education, ethnicity, biomedical variables (MAP, BMI, HDL cholesterol, triglycerides, fasting glucose, fasting insulin, diabetes, rheumatoid arthritis). Health behaviours (smoking, alcohol	Neither IL-6 nor CRP significantly predicted change in total BDI-II score, in cognitive-affective subscale score, or somatic-vegatative subscale score by follow-up.	No	

							intake, physical activity).			
Von Kanel 2009 [246]	Fibrinogen	Hospital Anxiety and Depression Scale (HADS), German Language version	Mean follow-up 21 months (range 13-27 months)	Linear regression	German school-teachers, 65% female, mean age 49, without diabetes at baseline	57	Gender, age, BMI, MAP (mean arterial pressure) were adjusted for in all analyses Additional analyses also adjusted for physical activity, alcohol intake and longitudinal change in MAP	Adjusting for gender, age, BMI and MAP, baseline fibrinogen at did not predict change in depressive symptoms (p=0.85).	No	Increases over the two years in fibrinogen and in depressive symptoms were significantly associated. However as the authors point out, causal direction cannot be inferred
Milaneschi 2009 [244] NB: there is another Milaneschi et al paper from 2012, which is a duplicate as far as this review is concerned	CRP, IL-1β, IL-1ra, TNF-α, IL-6, IL-6 receptor, IL-18	20-item version of the CES-D, with a cut-off of 20 for depressed mood. In additional analyses using a cut-off of 16, conclusions were not affected	Incident depressed mood was assessed at 3 and 6 years post-baseline	RRs for incident depressed mood by quartiles of inflammatory markers at baseline	Older Italian adults, (50.6% female, mean age 74.3, +-6.8), free of depressed mood at baseline	652 for 3-year analysis 597 for 6-year analysis	Age and gender, plus the following if they were associated (p=0.10) with incident depressed mood at the relevant follow-up assessment: years of education, BMI, hip arthritis, NSAID use, antidepressant use, hypertension, COPD, diabetes, ADL disabilities	Baseline IL-1ra was not associated with incident depressed mood at 3-year follow-up. However, it was associated with incident depressed mood over the whole period. Compared to the lowest IL-1ra quartile, for those	Hard to tell. The authors argue that IL-1ra is a reliable marker of inflammation since its production 'increases under the same conditions that stimulate Il-1α and Il-1β' but it	Participants lost to follow-up had significantly higher mean levels of inflammatory markers at baseline. This may have produced underestimates of effect size

								in the third quartile RR=1.7 (1.07-2.96), and for those in the highest quartile, RR=1.7(1.05-2.64) Baseline levels of markers other than IL1ra did not predict incident depressed mood at any point	remains in circulation for longer. That its predictive association with incident depression only emerged after 6 years is intriguing. The authors hypothesise that 'the influence of inflammation on the development of depressive symptoms is a slow process that takes several years to cross the threshold of clinical manifestation'	
Hamer et al 2009 [241]	CRP, fibrinogen	8-item version of	2 years	Logistic regression	English men (47.4%) and	4323	Baseline CES-D, age, gender, occupational	Each standard deviation increase	Yes when inflammatio	

		the CES-D. A cut-off of 4 was used to define depressive symptoms			women (52.6%) aged 63.4 +/-9.7 years, free from depression at baseline		class, presence of long-standing illness, smoking and alcohol consumption	in baseline CRP was associated with increased odds of depressive symptoms 2 years later: OR=1.32 (1.13-1.55) Baseline fibrinogen did not predict depression at follow-up	n is indexed by CRP, no when indexed by fibrinogen	
Prather 2009 [49]	IL-6 levels, pre-treatment and during treatment	Depressive symptoms measured by the Beck Depression Inventory, also incident Major Depressive Disorder as determined by the SCID-1 Sleep quality was measured by Pittsburgh Sleep Quality Index (PSQI)	Monthly assessments for 4 months after starting IFN-α treatment	Repeated-measure mixed-effect analyses to compare changes in IL-6 and BDI over time Cox regression for MDD incidence Hierarchical multi-level models to examine cross-lagged associations between depressive	Hepatitis C patients (67% male) being treated with IFN-α therapy Participants were at baseline free of mood, anxiety psychotic or drug/alcohol disorders, free of known inflammatory disorders others than HCV, and not taking medications known to	95	Age and weight, BDI score at the previous month	Patients above the median for pre-treatment IL-6 had an increased risk of developing MDD ($p<0.05$) Higher peripheral IL-6 levels across assessments, significantly predicted the next month's BDI scores ($p<0.0005$) Higher pre-treatment IL-6 (>1.25pg/mL) predicted higher BDI scores over the course of	Yes. Additional analyses suggest poor sleep quality may partially mediate the association between IL-6 levels and incident MDD	Robust evidence for a bidirectional association, but it is not clear whether results can be generalized beyond this population

				symptoms, sleep quality and IL-6	affect the immune system			treatment ($p<0.05$)		
Matthews et al 2010 [236]	CRP	CES-D	Annual assessments over a 7-year period	Linear regression: lagged models examined influence of CRP at year X on CES-D at year X+1 and vice-versa	Pre- or peri menopausal women, mean age 46.2 (range 42-52). At baseline participants were not taking steroids/ inhaler and had none of the following: stroke, heart condition, diabetes, arthritis/ osteoarthritis, osteoporosis	1781	Baseline education, race/ethnicity, study site. Year X CES-D, age, smoking, physical activity, BMI, waist circumference, menopausal status, hormone use, physical activity, smoking. Year X presence of stroke, heart condition, high blood pressure, diabetes, thyroid condition, arthritis/ osteoarthritis, osteoporosis. Year X use of insulin, medication for heart disease, arthritis or nerves/depression, hormones, inhaler/steroids. Year X and year X+1 values of the following: morning blood draw, fasting blood draw	In fully-adjusted lagged models, CRP at year X significantly predicted higher CES-D score at year X+1 ($p=0.03$)	Yes	
Janicki Deverts et al 2010 [238]	CRP	20-item version of the CES-D. Additional	5 years	Linear regression	Mean age at baseline: 40.2, 55% female, 41.8% black	2544	Baseline CES-D, age, sex, race, and the following measured at follow-up: education, BMI, SBP,	In adjusted models baseline CRP did not predict total or sub-scale scores	No	

		analyses used four subscales measuring depressed affect, positive affect, somatic symptoms and interpersonal problems					glucose, insulin, HDL and LDL cholesterol, triglycerides, smoking, alcohol intake, physical activity, oral contraceptive and HRT use, total number of diagnosed conditions and total number of inflammation-related medications	for depressive symptoms at follow-up among black participants, white participants, or in the whole sample		
Pasco 2010 [50]	CRP	*De novo* MDD during the 10-year follow-up, identified retrospectively by the Structured Clinical Interview (SCID-I/NP) at year 10	10 years	Cox regression	Australian women aged 20-84 at baseline with no history of major depression	644	Age (used as the time axis), weight, current smoking, NSAID use	HR for de novo MDD: 1.44(1.04-1.99), p=0.026 per standard deviation increase in log CRP. 'Adjustment for lifestyle factors, comorbid disease and medications did not explain this association'	Yes	Retrospective assessment of episodes of Major Depression meant that recall errors may have limited accuracy of age of onset
Wirtz 2010 [243]	CRP, IL-6, sICAM-1	21-item Beck Depression Inventory (BDI)	Linear regression	12 months, plus 18 months for a subsample of 16 patients.	Heart failure patients (mean age 60.8, 86.7% men) without a myocardial infarction in the past month, recent	30	Baseline BDI score Baseline age, gender, BMI, mean arterial pressure, indicators of heart failure severity and medication use were not included in	Only sICAM-1 at baseline significantly (p=0.04) predicted follow-up BDI score Neither baseline CRP nor baseline	No for CRP and IL-6. For sICAM-1, interpretation depends on what this actually does; in any	

					stroke or neurological impairment, severe COPD, or psychiatric illness other than anxiety or depression.		multivariate models since they did not show significant associations with depressive symptoms at follow-up	IL-6 predicted BDI score 12 months later in linear regression Among subjects with baseline CRP>3mg/L, higher CRP predicted higher BDI scores at 12 months Among the subset of 16 patients followed for 18 months, baseline sICAM-1 did not predict BDI score at 18 months significantly (p=0.10)	case it is unclear whether results are generalizable beyond heart failure patients	
Luukinen 2010 [242]	CRP	Short Zung Self Rating Depression Scale, SZSRDS. Depressed mood was defined as an SZSRDS score of ≥28	2.5 years	Logistic regression for incident depressed mood	Men and women aged 70 and over (61% female), free of depressed mood (SZSRDS score ≥28) or anti-depressant use at baseline	404	Age, medically treated diabetes, BMI, MMSE result, a cardiovascular event during follow-up, current smoking. Results were stratified by gender	Compared to the baseline CRP group (<1mg/L), men with CRP ≥3mg/L had an OR of 5.2 (1.1-24.7) for incident depressed mood. No significant associations were found for women	Yes, at least for men in this age group. Authors suggest underrepresentation of older women may have biased	The authors point out that deaths during follow-up may have produced underestimation of effect sizes, since elevated CRP is associated with mortality

									results.	
Duivis et al 2011 [247]	CRP, IL-6, fibrinogen	The 9-item PHQ (Patient Health Questionnaire), with a cut-off of 10 for depressive symptoms	Assessments at baseline and then annually for 5 years	Linear regression (mean PHQ score across interviews on baseline CRP, IL-6 fibrinogen) Logistic regression (number of times above cut-off on baseline CRP, IL-6, fibrinogen)	Patients with coronary heart disease, mean age 66 % male not given)	667	Baseline values of: PHQ, age, gender, education, race, BMI, physical activity, current smoking, aspirin use, history of diabetes, myocardial infarction, congestive heart failure	Baseline CRP, IL-6 and fibrinogen did not predict depressive symptoms over follow-up (either mean score or number of times above cut-off) in any model	No	
Thomsen 2012 [52]	CRP, fibrinogen and leukocyte count	Hospital admission for depression	5 years	Cox regression with age as time scale	Danish COPD patients who had not been hospitalized for depression before, 53% female, mean age 65 (range 57-74)	8656	Age, sex, smoking status, cumulative tobacco consumption (pack-years) in all models plus BMI, hypertension, cholesterol, triglycerides and HDL cholesterol in additional models	Risk of hospital admission for depression did not increase with levels of CRP, fibrinogen or leukocyte count. Patients with elevated levels of one, two or three of the biomarkers were not at increased risk compared to those with elevated levels of none	No, at least not for this population. The authors suggest that systemic inflammation in COPD masks some of the associations found in healthy individuals. The lack of association	Crude outcome measure; also results may not be generalizable beyond COPD patients

									could also be due to the fact that hospitalization is a very crude measure of depression	
Shaffer et al 2011 [221]	CRP	21-item Beck Depression Inventory (BDI), and its cognitive-affective and somatic-affective subscales	3 months: baseline measurements were taken during hospitalization, follow-up was at 1 and 3 months later	Cross-lagged path models using CRP and BDI measurements from the three assessments	Post-acute coronary syndrome patients, mean age 59.6 (S.D. 12.7), 43.6% female	163	Age, sex, education, race/ethnicity, BMI, antidepressant use, smoking status, history of: diabetes or rheumatic condition	CRP at baseline did not predict BDI at 1 month, nor did CRP at 1 month predict BDI at 3 months	No, at least not for this patient population	
Archer 2012 [237]	CRP, IL-6, TNF-α	Hospital Anxiety and Depression Scale (HADS)	24 weeks: HADSD taken pre-surgery and 1, 6, 12 and 24 weeks post-surgery	Univariate and multivariate regression	Cancer patients undergoing surgery. These were 56 head and neck cancer patients (mean age 70, 43% female) and 34 colorectal cancer patients (mean age 63, 51% female).	90	Baseline HADS score, tumour stage, chemotherapy. Confounding factors such as age, sex, smoking, comorbidity, BMI and alcohol could not be included in multivariate models due to insufficient power. The authors report that none 'significantly changed results' when	No associations with HADSD scores during follow-up of baseline inflammatory markers were found among head and neck cancer patients. Among colorectal cancer patients only, baseline CRP and TNF-α levels were positively associated with HADS score over	Possibly for colorectal cancer patients, but results are undermined by lack of adjustment for confounders Associations became non-significant with adjustment for	

							included singly	repeated measures. No significant associations were found with IL-6. However, these associations disappeared when childhood trauma was taken into account.	childhood trauma, suggesting any association may have been confounded by early life events Conclusions may not be generalizable beyond cancer patients undergoing surgery	
Baune 2012 [245]	CRP, IL-1β, 1L-6, 1L-8, 1L-10 and 1L-12p70, sVCAM-1, PAI-1 and SAA	15-item Geriatric Depression Scale (GDS). A cut-off of 6 was used to define caseness	2 years	Linear and logistic regression	Men (44.8%) and women (55.2%) aged 70-90 at baseline	1037	Gender, age, years of education, smoking, BMI, current use of NSAIDs, statins or antidepressants, total number of diagnosed medical disorders, cardiovascular disorders, diabetes, endocrine disorders	Baseline IL-8 levels were positively associated with GDS score at follow-up (p=0.04), while baseline 1L-12p70 and follow-up GDS score were inversely associated (p=0.01)	Hard to tell, since it would appear that these models were not adjusted for GDS score at baseline	Also, results may not be generalizable beyond elderly populations since, as they authors stress, the aetiology of geriatric depression may be distinct

9.1.2 Appendix B: Summary of longitudinal studies investigating depression to inflammation										
Author and Year	**Inflammatory markers used**	**Depression measure used**	**Follow-up**	**Analysis type**	**Population**	**N**	**Covariates**	**Result**	**This direction supported?**	**Limitations**
Glaser 2003 [234]	IL-6	Beck Depression Inventory-Short Form (BDI-SF)	14 days	Repeated-measures linear regression	Older adults (43 men, 76 women) aged 48-89 (mean age 71.2) undergoing influenza vaccination	119	Baseline BDI-SF, caregiver status, ethnicity, education, weight, alcohol intake, plus cardiac medication and B-blockers in additional models Sex, age, smoking, exercise, vaccine history were not included since they were not associated with IL-6 or BDI score Other medications were not included since their use did not appear related to IL-6	IL-6 levels in the whole sample did not increase during follow-up (no main effect on IL-6 for vaccination) A time by depressive symptoms interaction (p=0.02) indicated that plasma IL-6 did increase during follow-up for individuals with greater depressive symptoms at baseline This interaction was robust against further adjustment for cardiac medication and β-blockers (p=0.008)	Since a control group was not included, we cannot tell if there would have an increase in IL-6 for those with greater baseline depressive symptoms in the absence of vaccination. Hence, this does not support a main effect of depression on later inflammation, but may support an interactive effect. The authors interpretation is that in older adults, depression may sensitize the inflammatory response to infection and other challenges	
Kiecolt-Glaser 2003 [229]	IL-6	13-item Beck Depression Inventory	6 years	This was a study into the impact of caregiving on	160 caregivers and controls: 65 men and			BDI did not significantly predict the IL-6	No	

		(BDI)		change in IL-6; depressive symptoms were considered as a possible confounder/mediator	160 women, mean age 70.6 (range 55-89)			slope.		
McDade 2006 [248]	CRP	20-item version of the CES-D	3 years	Linear regression	Representative sample of adults from Chicago, aged 50-67 at baseline	188	CES-D from the year before (hence, isolating association of CRP with recent CES-D change) age, gender, ethnicity, smoking, adiposity, time to fall asleep, medication use, alcohol consumption, diet	A trend (p=0.057) was found towards higher CRP with increasing depressive symptoms	Not really. Since CRP the year before was not included in the models, directionality cannot be inferred	
Gimeno et al 2008 [235]	IL-6 and CRP	A four-item sub-scale of the General Health Questionnaire measuring cognitive symptoms of depression only	11.8 years (mean)	Path analysis	British civil servants. Mean age 50, 30% female	3339 to 3370	Baseline CRP/IL-6, sex, employment grade, ethnicity, alcohol intake, diet, physical activity, smoking, blood pressure, BMI, waist:hip ratio, total:HDL cholesterol ratio, CHD, type 2 diabetes, respiratory illness, medications (CHD, diabetes and central nervous system medication,	Cognitive symptoms of depression at baseline did not predict either CRP or IL-6 at follow-up.	No, at least not for cognitive symptoms of depression	

							anti-depressants, analgesics, female sex hormones).			
Rohleder 2008 [225]	IL-6 and CRP	10-item version of the CES-D	20 weeks	hierarchical linear regression	Young women, mean age 18.6 (SD: 1.4, range: 16.1–20.9)	65	Age, BMI, baseline IL-6/CRP	Neither trait nor state depressive symptoms predicted IL-6, but deviation of state from trait depressive symptoms did (p=0.03). No significant associations were found for CRP	Results suggest that in this age group, depressed mood *relative to the individual's usual mood* has a short-term effect on the fast-reacting IL-6, but not in the more stable CRP.	All participants were young women. The authors suggest that longer-term effects of depression on inflammation may not be visible in this population because 'allostatic load is a process that needs several years or decades to develop and exert its negative effects'
Hamer et al 2009 [65]	CRP and fibrinogen	8-item CES-D scale	2 years	General linear models, mediation analysis	English men (46.5%) and women (53.5%), age 60.5+/-9.2 years)	3609	Age and sex, weight change, waist increase, alcohol consumption, smoking, physical activity	Baseline CES-D showed both direct and indirect (via health behaviours) associations of baseline CES-D with CRP at follow-up (both p<0.05). Associations of	Results are consistent with inflammation being influenced by depression via health behaviours However lack of adjustment for baseline inflammation undermines	Baseline CRP and fibrinogen could be included as covariates, so reverse causation cannot be ruled out

								baseline CES-D with follow-up fibrinogen were entirely explained by health behaviours	strength of conclusions	
Stewart et al 2009 [239]	IL-6 and CRP	Beck Depression Inventory (BDI-II). Cognitive-affective and somatic-vegetative subscales were also examined	6 years	Path analysis	Mean age 61.0, 51.7% female	263	Baseline IL-6/CRP. Baseline age, gender, education, ethnicity, smoking, alcohol intake, physical activity, BMI, MAP, HDL cholesterol, triglycerides, fasting glucose, fasting insulin, diabetes, rheumatoid arthritis.	Baseline BDI-II predicted change in IL-6 (p=0.01) IL-6 change was significantly (p=0.03) predicted by the somatic-vegetative subscale but not the cognitive-affective subscale. Neither total BDI-II score nor either subscale predicted change in CRP	Yes for IL-6, no for CRP The overall association for IL-6 appeared driven mostly by somatic-vegetative symptoms, although the coefficients were not significantly different	*Combined with the results of Gimeno, this is consistent with a model in which different symptom clusters are causally involved at different stages*
Prather 2009 [49]	IL-6 levels, pre-treatment and during treatment	Depressive symptoms measured by the Beck Depression Inventory	Monthly assessments for 4 months after starting IFN-α treatment	Repeated-measure mixed-effect analyses to compare changes in IL-6 and BDI over time	Hepatitis C patients (67% male) being treated with IFN-α therapy Participants	95	Age and weight, IL-6 score at the previous month	BDI scores at a given month significantly predicted IL-6 levels at the next month (p<0.05)	Yes – although changes in health behaviours between each pair of assessments, which were not controlled for,	

		Sleep quality was measured by Pittsburgh Sleep Quality Index (PSQI)		Hierarchical multi-level models to examine cross-lagged associations between depressive symptoms, sleep quality and IL-6	were at baseline free of mood, anxiety psychotic or drug/alcohol disorders, free of known inflammatory disorders others than HCV, and not taking medications known to affect the immune system			There was also a trend (p=0.051) for baseline BDI to predict overall IL-6 levels during follow-up There was no evidence of mediation by sleep disturbance, since BDI score did not predict PSQI score	could contribute to this relationship	
Von Kanel 2009 [246]	Fibrinogen	German-language version of the Hospital Anxiety and Depression Scale HADS-D	Mean follow-up was 21 months (range 13-27 months)	Linear regression	German schoolteachers, 65% female, mean age 49 at baseline	57	Baseline gender, age, BMI, MAP (mean arterial pressure) were controlled for in all analyses Additional analyses also controlled for behavioural factors (physical activity and alcohol consumption) and longitudinal change in MAP	No significant associations were found between baseline depressive symptoms and change in fibrinogen over time	No	Increases over the two years in fibrinogen and in depressive symptoms were significantly associated. However as the authors point out, causal direction cannot be inferred
Matthews et al 2010 [236]	CRP	CES-D	Annual assessments over a 7-year	Linear regression: lagged models	Pre- or peri menopausal women, mean	1781	Baseline education, race/ethnicity, study site. Year X	In initial models adjusting for year X CRP and	The authors argue that the trend (p=0.10) towards	

			period	examined influence of CRP at year X on CES-D at year X+1 and vice-versa	age 46.2 (range 42-52). At baseline participants were not taking steroids/ inhaler and had none of the following: stroke, heart condition, diabetes, arthritis/ osteoarthritis, osteoporosis		CRP, age, smoking, physical activity, BMI, waist circumference, menopausal status, hormone use, physical activity, smoking. Year X presence of stroke, heart condition, high blood pressure, diabetes, thyroid condition, arthritis/ osteoarthritis, osteoporosis. Year X use of insulin, medication for heart disease, arthritis or nerves/depression, hormones, inhaler/steroids. Year X and year X+1 values of the following: morning blood draw, fasting blood draw	demographics only, higher CES-D scores at year X predicted higher CRP scores at year X+1 (p=0.02). In adjusted models, the association was no longer significant (p=0.10)	significance for this direction supports a weak bidirectional relationship. The significant association adjusting only for baseline CRP and demographics may support the mediation by health behaviours model	
Janicki Deverts et al 2010 [238]	CRP	20-item version of the CES-D. Additional analyses used four subscales measuring	5 years	Linear regression	US adults (55% female, 41.8% black) mean age at baseline: 40.2	2544	Baseline CRP, age, sex, race, and the following measured at follow-up: education, BMI, SBP, glucose, insulin, HDL and LDL cholesterol,	In adjusted models, baseline CES-D score predicted CRP at follow-up in the whole sample (p<0.05).	Yes, since a robust association was found in the whole sample. Analysis using four sub-scales of the	The authors suggest the disparity in the association by race may result from the fact that CES-D scores were

		depressed affect, positive affect, somatic symptoms and interpersonal problems					triglycerides, smoking, alcohol intake, physical activity, oral contraceptive and HRT use, total number of diagnosed conditions and total number of inflammation-related medications	Among black participants only (N=1063), the association was stronger (p<0.001), while among white participants only (N=1481) it was non-significant	CES-D suggested positive affect and somatic symptoms drove the association, rather than depressed affect and interpersonal problems	higher and more variable in black compared to white participants
Duivis et al 2011 [247]	CRP, IL-6, fibrinogen	The 9-item PHQ (Patient Health Questionnaire), with a cut-off of 10 for depressive symptoms	Assessments at baseline and then annually for 5 years	MANCOVAs to evaluate effect of depressive symptoms on a single index of inflammation at follow-up Linear regression of CRP, IL-6 and fibrinogen at follow-up on mean PHQ score across all interviews Linear regression of CRP, IL-6 and fibrinogen at follow-up on number of times above	Patients with coronary heart disease, mean age 66 (% male not stated)	667	Age, gender, education, race, BMI, physical activity, current smoking, aspirin use, history of diabetes, myocardial infarction, congestive heart failure	Adjusted for demographics and medical variables, number of times above PHQ cut-off predicted higher IL-6 (p=0.01) but not CRP or fibrinogen. Mean PHS score across all assessments predicted Il-6 and CRP, but not fibrinogen, at follow-up MANCOVAs adjusting for demographics, medical	Possible evidence for impact of depression on later inflammation, if mediated by health behaviours. However, only some of these models adjusted for baseline levels of inflammatory markers. Models examining change in inflammatory markers over 5 years in relation to number of times above cut-off over 5 years found no associations	

				cut-off across all interviews.				variables and baseline inflammation found that depressive symptoms predicted subsequent overall inflammation (p=0.02) These all became non-significant after adjustment for health behaviours		
Shaffer et al 2011 [221]	CRP	21-item Beck Depression Inventory (BDI), and its cognitive-affective and somatic-affective subscales	3 months: baseline measurements were taken during hospitalization, follow-up was at 1 and 3 months later	Cross-lagged path models using CRP and BDI measurements from the three assessments	Post-acute coronary syndrome patients, mean age 59.6 (S.D. 12.7), 43.6% female	163	Age, sex, education, race/ethnicity, BMI, antidepressant use, smoking status, history of: diabetes or rheumatic condition	Greater depressive symptoms at baseline predicted smaller decreases in CRP from baseline to 1 month ($p<0.05$), but depressive symptoms at 1 month did not predict CRP change between 1 and 3 months.	Possibly, although the lack of association of 1-month BDI with 3-month CRP undermines this. Subgroup analyses suggest this direction may be mostly driven by cognitive-affective symptoms This study looked at rate of decline in inflammation after hospitalization for	

								CRP at 3 months was predicted by baseline cognitive-affective symptoms ($p<0.001$), but not baseline somatic-affective symptoms	acute coronary syndrome; hence results cannot be generalized to healthy adults	
Copeland et al 2012 [51]	CRP	Structured clinical interviews: the Child and Adolescent Psychiatric Assessment until age 16, and the Young Adult Psychiatric Assessment thereafter	Up to 12: Three cohorts of children, aged 9, 11 and 13 at intake, were assessed annually until age 16 and then again at 19 and 21	Linear regression, in which CRP at each wave was regressed on depressive symptoms/diagnoses/cumulative depressive episodes at the previous wave	Three cohorts of children aged 9, 11 and 13 at intake from 11 counties in North Carolina	5810 blood spots from 1334 participants	Time since last assessment, CRP at the last assessment, age, sex, race, BMI (adjusting for age and sex for under-20s), medication use, recent use of alcohol, nicotine and illicit drugs, low socioeconomic status, physical ailments in past 12 months	In adjusted models, neither depressive symptoms nor depressive diagnoses predicted later CRP, but number of cumulative episodes did ($p=0.02$). Mediation analyses indicated that smoking (Sobel $p=0.02$), BMI (Sobel $p=0.01$) and infections (Sobel $p=0.009$) partially mediated this association, although in	Yes. That a significant association was found only for cumulative depressive episodes, but not symptoms or diagnoses at the last assessment, suggests chronicity may be important. Mediation analyses indicate part of the effect is via health behaviours	

								each case the direct path remained significant (p<0.01)		
Baune 2012 [245]	CRP, IL-1β, 1L-6, 1L-8, 1L-10 and 1L-12p70, sVCAM-1, PAI-1 and SAA	Geriatric Depression Scale (GDS), 15-item version. A cut-off of 6 was used to define caseness	Retrospective assessment of remitted - i.e. past but not current - depression. This was defined as a history of a depressive episode requiring medical attention but <6 GDS score at baseline	Logistic regression	Men (44.8%) and women (55.2%) aged 70-90 at baseline	1037	Gender, age, years of education, smoking, BMI, current use of NSAIDs, statins or antidepressants, total number of diagnosed medical disorders, cardiovascular disorders, diabetes, endocrine disorders	Remitted depression at baseline (N=137) was associated with baseline PAI-1: OR=1.37, CI=1.10-1.71, p=0.005 (*doesn't specify PAI-1 categories used here*).	Since PAI-1 was associated with higher for participants with previous but not current depression, results are consistent with an influence of earlier depression on later PAI-1. However, lack of adjustment for PAI-1 at the time of prior depression, and a comparison group including people with current AND past depression, undermines this interpretation	Also, results may not be generalizable beyond elderly populations; the authors stress that the aetiology of geriatric depression may be distinct
Kupper 2012 [249]	CRP, IL-6, TNF-α, IL-1ra, sTNFR1, sTNFR2	Cognitive/affective and somatic/affective depressive symptoms, measured by subscales of the 21-item Beck Depression	12 months	Linear regression, with both baseline depressive symptoms and change in depressive symptoms entered in the same model	Dutch heart failure patients (73% male) who at baseline were aged 65.4 (+-8.7), and free of serious psychiatric illness other	110	Age, gender, BMI, disease severity (New York Heart Association functional class, LVEF, 6-minute walk test), change in disease severity (change in 6MWT), change in	Baseline cognitive/affective symptoms of depression were associated with increase in sTNFR1 and sTNFR2 by follow-up (both p<0.05)	Lack of significant associations for CRP, IL-6, TNF-α and IL-1ra imply no predictive relationship, but significant predictions were found for sTNFR1 and sTNFR2.	

		Inventory (BDI-I)			than mood disorders, other life-threatening illness, and had not had a myocardial infarction in the last month		depressive symptoms, psychotropic medication use, HF aetiology in all models. Additionally, smoking, statin use and aspirin use were included for models with Il-6 and CRP.	Increase in somatic/affective symptoms over 12 months was associated with sTNFR2 at follow-up (p=0.008). No other associations were significant	However, since it would appear that baseline levels of inflammatory markers were not included as covariates, no conclusions can be made as to the causal direction	
Archer 2012 [237]	CRP, IL-6, TNF-α	Hospital Anxiety and Depression Scale (HADS)	24 weeks: HADSD taken pre-surgery and 1, 6, 12 and 24 weeks post-surgery	Univariate and multivariate regression	Cancer patients undergoing surgery. These were 56 head and neck cancer patients (mean age 70, 43% female) and 34 colorectal cancer patients (mean age 63, 51% female).	90	Baseline HADS score, tumour stage, chemotherapy. Age, sex, smoking, comorbidity, BMI and alcohol could not be included in multivariate models due to insufficient power Authors report that none 'significantly changed results' when included singly	No significant associations were found of HADS score at baseline with inflammation during follow-up	No	

9.2 APPENDICES RELATING TO CHAPTER 3: DATA AND METHODS

9.2.1 Appendix C: Procedure for updating the NCDS Activity Histories dataset

9.2.1.1 General principles

9.2.1.1.1 Current vs. retrospective reports

In the updating process, a number of considerations were taken into account but one principle trumped: that current reports are likely to be more accurate than retrospectively given reports. Hence, while an activity reported to be current at the biomedical sweep itself also took precedence over a retrospectively-given report in the AHD of different activity covering that period, the reported start date of the current activity at the AHD was only trusted if it did not conflict with a report of a different current activity in the AHD.

Similarly, earlier retrospective accounts (e.g., of an activity start date) were in almost all cases given precedence over later retrospective accounts. The only exception was where using the earlier account would mean erasing entirely another activity reported as a past activity at a later sweep. In other words, it was assumed that while earlier retrospective reports are likely to be more accurate than later ones, misremembering a start date at an earlier point is more likely than later imagining that an event occurred which did not.

9.2.1.1.2 Keeping to the rules of the original AHD

It was decided that rules used in the construction of the original AHD should be adhered to as much as possible. These rules, described in full in the AHD user guide[21] concern assumptions such as by how many months two activities' start dates can differ for them to be assumed duplicates under certain sets of conditions.

9.2.1.1.3 Rounding of durations

Like in the original AHD, all start and end dates were considered in months and years, with all calculations made at this level of detail. This was a response to the large amount of missingness, and

expected inaccuracies in nonmissing reports, of the date on which activities began or ended. However, in contrast to the rules of the original AHD, activities which started and ended in the same month were assigned a duration of 1, as opposed to 0. It was decided that while the durations of these activities were unclear, if these activities had been memorable enough to be reported they should count a minimum amount towards summary measures.

9.2.1.1.4 Currentness of incoming/outgoing activities

Where there was a changeover in activities in the month when the biomedical interview took place, the outgoing activity was considered 'current' according to the AHD, rather than the incoming activity. This was because of a general assumption that the outgoing activity is more likely to have exerted any biological effects than the incoming activity, and is therefore more relevant for classifying exposure.

9.2.1.1.5 Pre-existing negative-duration activities

A number of existing errors in the AHD which pre-dated my updating process had to be fixed. Activities whose end dates had been reported as prior to their start dates were assigned an end month equal to the start month and the minimum duration of 1. A small group of activities reported as current had a start date one month after the interview at which they were reported. To avoid negative-duration activities, the changeover from the preceding activity was moved back by one month.

9.2.1.1.6 Censoring

The last reported activity in each participant's sequence was censored at the date of the last interview at which they were present, even if no activity data was given at the later point. Hence for a small number of participants who had data on my outcomes of interest (inflammatory markers at age 42 or MI score at 50) but whose last report of an activity was a current activity from a previous sweep, it was assumed to still be current at outcome measurement.

9.2.1.2 Discrepancy classifications and their update procedures

The updating process took one of two general forms. The first involved shifting the end of the preceding activity/start of the subsequent activity in the AHD if this would remove the discrepancy without overriding a current activity in the AHD from another sweep; the second involved insertion of an entirely new activity into the AHD sequence at the time of the biomedical sweep. This could firstly be between two existing activities whose end/start dates were modified to make room for the new activity, such that the participants' number of total activities increased by one. The insertion could also be made into the middle of a longer-running activity such that the total number of activities for that person increased by 2. Since most cohort members had far less than 33 activities in their histories, the later blocks of variables were largely empty, and where new activities were inserted the information corresponding to the remainder of that participant's activity sequence was shifted up through 1 or 2 blocks of variables as appropriate. The details of the process, including the calculation of start and end dates where reports contradict each other, was determined by a further set of hierarchical rules described in the following sections.

A note on the notation: in the following section, the activity in the original AHD sequence during which the biomedical assessment supposedly fell is the Nth activity. The activity immediately preceding this is the N-1 activity, and the activity immediately following it is the N+1 activity. The activity after that is the N+2 activity, and so on. The activity reported as current at the biomedical sweep is referred to as the biomedical activity.

9.2.1.2.1 A new report for participants who had dropped out

In the construction of the original AHD, activities reported as current were allowed to run until either an end date was reported, or a new activity was reported to start which was incompatible with the previous one. This meant that for X participants who gave no new information on activities at sweep 7 or 8, the activity coded as current as of the biomedical sweep was an old one reported at sweep 6 or earlier even if it had in fact finished. In these cases, I truncated that activity at either the

date that the biomedical activity was reported to start (so long as that would not result in erasing entire activities from the AHD) or the month of biomedical assessment (where the start date of the biomedical activity was missing, or seemed unreliable because it would result in erasing whole previous activities from the AHD). I then inserted the biomedical activity as a new activity in the history immediately after, which was censored at the last sweep at which the participant was present.

9.2.1.2.2 Misremembered start or end dates

It seemed plausible that many discordant accounts would be explained by people slightly misremembering start or end dates when reporting activities retrospectively at sweep 7 or 8. This would predict many discrepant cases where the account of current activity given at the biomedical sweep matched, in the AHD, the activity either immediately preceding or immediately following the supposedly current activity – the N-1 or the N+1 activity. But since the overarching heuristic in this exercise was that current reports must take precedence over retrospective reports, and recent retrospective reports over more distant ones, additional conditions also needed to be met before this assumption could be made. In cases where the 'real' current activity appeared to be N-1 in the AHD sequence, the end date of the N-1 activity was only deemed negotiable and moved forward to include the month of biomedical interview if it had been reported as part of a past activity at sweep 7 or 8. If the end date of the N-1 activity had been reported at sweep 6 (i.e., the N-1 activity was reported as a past activity at sweep 6), this was not an option. The end of this activity could not be moved forward to the biomedical sweep, because as of sweep 6 it was known to be in the past.

In essence, this meant assuming the biomedical activity and the N+1/N-1 activity were duplicates. In the construction of the original AHD, two activities could be assumed to be duplicates if their start dates were no more than either 6 or 14 months apart, depending on whether one activity is missing and end date, and if so whether the earlier or the later. Using these rules, I therefore identified cases where the biomedical activity and the N-1 activity could be assumed to be duplicates, and updated

the AHD by moving the changeover between the N-1 and Nth activities forwards to the month of biomedical assessment. Where the biomedical activity and the N+1 activity could be assumed to be duplicates, the changeover between the Nth activity and N+1 activity was moved back to the month when the biomedical activity was reported to start, or the month of biomedical assessment if that was missing.

9.2.1.2.3 The same activity, described in a slightly different way

The largest group of discrepancies (N=645) were cases where the discrepant activity types were not identical, but were very similar. For these 645 participants, I judged discrepancies to result from the cohort member referring to the same activity in a slightly different way at the two time points, and hence that the AHD did not need to be updated for this group.

These combinations were:

1. full-time employment/part-time employment,
2. full-time self-employment/part-time self-employment,
3. full-time employment/full-time self-employment,
4. full-time self-employment/part-time self-employment,
5. full-time education/part-time education, and
6. temporarily sick or disabled/permanently sick or disabled

It is quite plausible that these discrepancies result from participants classifying the same activity slightly differently on the two interview occasions (e.g. a job which is 4 days/week could be judged as part-time or full-time; contractors working for one company at a time are effectively employees of that company, although for tax purposes they are self-employed).

9.2.1.2.4 Fluidity in self-definition: emphasising one of multiple roles

For a much smaller group (N=87), the combination of activities meant the discrepancy appeared to result from fluidity of self-definition, such that a person with multiple roles had emphasised one as their 'main' activity as of the biomedical sweep, and a different one as their 'main' activity at that

time in the retrospective account given later. This group mostly comprised a cluster of 51 women who in one account had 'looking after home or family' and in the other account 'part-time employed' or 'part-time self-employed'. Given the prevalence of part-time work among women with families, it seems highly plausible that for these women the accounts were not mutually exclusive, that both were in some sense true. Smaller groups suggested fluidity of self-definition between two non-work categories, notably 20 people with a discrepancy between being out of the labour force due to sickness or disability and looking after home or family. Interestingly, a handful of further discrepancies included an account of unemployment, with an apparent gendered aspect to the identification other than as a jobseeker. While 12 women and 2 men had a discrepancy between unemployment and looking after home or family, 10 men and 3 women had a discrepancy between unemployment and being permanently sick or disabled.

For these 87 cases, it was decided again that no real discrepancy existed, since the most likely explanation was that both accounts were accurate in different ways. However, a condition of this, according to the rules used in the construction of the AHD for assuming two activities to be duplicates, was that the activity periods had to have similar start dates. 'Similar' was here defined as 14 months' difference or less, since this was the greatest discrepancy in start dates allowed for any type of duplicate as specified in the original rules for the AHD.

9.2.1.2.5 Activity spells completely forgotten: activities with no possible match in the AHD

For remaining discrepant cases which did not fit the specifications for any of the groups above, current activities from the biomedical sweep were assumed not to not exist in any form anywhere in the AHD because they had been forgotten by the next non-biomedical sweep. They would need to be inserted as new activities into the participant's existing AHD sequence.

The month of biomedical interview was used for the end date of the new activity, since this was the last time the activity was ever mentioned – the approach was therefore conservative regarding duration of the new activity. When a new activity was inserted into the AHD sequence, it was

flagged as an activity only reported at the biomed sweep, for future users of this dataset. This was done by assigning a code of 999 for the activity-level variable *jslot*, indicating the sweep at which the activity was reported and whether it was current or past. Because only a few things were known about these new activities (start and end date, activity type) the other details present for activities reported at any other time (such as RGSC codes) were coded as missing.

These discrepancies were divided into eight subtypes, depending on factors such as whether the biomedical activity was entirely bounded by a single activity in the AHD or overlapped across multiple activities, whether the start date for the biomedical activity was missing, and whether non-missing start dates could be used without another existing activity being entirely erased. These procedures all resulted in the total number or activities being increased by either one (where a new activity was inserted between two existing activities) or two (where it was inserted into the middle of an existing sequence by splitting that in two).

The exact procedure for each subtype is described below.

9.2.1.3 Procedure for updating the NCDS AHD for each subgroups of new insertion

9.2.1.3.1 New insertions type 1:

Where the biomedical activity was entirely bounded by an existing activity in the AHD, it was inserted as a new activity using its reported start date as the start date and the date of biomedical assessment end date. This meant splitting the existing activity into a first and a second half, either side of the newly inserted activity. As a result, information on activities subsequent to the second half of the original activity were bumped up through two 'blocks' of activity variables; for example the information on the 12th activity in a person's history, initially contained in the set of variables suffixed with as 12, would be moved to the variables corresponding to the 14th. The person-level variable of total number of activities was also increased by two.

Where no start date for the biomedical activity had been given, the date of biomedical interview was used as the start date as well as the end date for the new activity, and a minimum duration of 1 month assigned. Again, this was being maximally conservative regarding the influence of the new activity. All activities subsequent to the right were bumped up through two blocks of variables, and the total number of activities increased by two.

9.2.1.3.2 New insertion type 2:

If the Nth activity in the AHD activity was reported at sweep 7 or 8 as a previous activity which started prior to the biomedical activity, but ended in the month of biomedical assessment, only one new activity was inserted into the sequence. Since the month of biomedical assessment is assumed to be the end date for these new insertions, the end dates of the Nth and biomedical activities are identical. In these cases the Nth activity was truncated to end in the month when the biomedical activity began and the biomedical activity inserted in the N+1 slot. Subsequent activities were pushed up through one block of variables, and the total number of activities increased by one.

9.2.1.3.3 New insertion type 3.1, 3.2, 3.3:

If the biomedical activity was not entirely bounded within the Nth activity, but rather the two overlapped with the biomedical activity starting first, the discrepant activities were sequenced to remove the overlap. The exact procedure depended on whether a) using the biomed start date would result in entire activities being erased from the AHD and b) the extent to which the end date of the N-1 activity was negotiable. Overlapping observations were therefore split into three subgroups:

If the reported start date of the biomedical activity fell within the N-1 activity, but subsequent to any sweep at which the N-1 activity was reported as current, the N-1 activity was truncated to end the month when the biomedical activity started. The biomed activity was inserted from here until the date of biomedical assessment. The former Nth activity was bumped into the N+1 slot, with its start

date pushed forwards to the month of biomedical assessment. All subsequent activities get bumped through one slot, and the total number of activities goes up by one.

For another group, the biomedical activity was reported to start during the N-1 activity at a date which preceded the sweep 6 interview. However, we know that the N-1 activity was current as of sweep 6, and therefore its end date cannot be pushed back before this as the biomedical start date would demand. Reconciling the two accounts, the N-1 activity is pushed back to the month of sweep 6 interview, and the biomedical activity inserted to start that month and run until the biomedical assessment. The Nth activity gets bumped into the N+1 slot, with its start date pushed forwards to the month of biomedical assessment. All subsequent activities get bumped through one slot, and the total number of activities for the cohort member goes up by one.

Where the biomedical activity start date fell during the N-2 activity or earlier, then inserting the biomedical activity using this start date would mean erasing entire activities from the history. In these cases, the start date given at the biomedical sweep was deemed highly unreliable and treated as if it were missing: the month of biomedical assessment was used as both the start and end date when the new activity was inserted into the sequence, resulting in a minimum-duration activity. As with new insertion type 1, a new activity has been inserted within an existing one, splitting it in two. All activities from the former N+1 activity onwards therefore get bumped up through two slots, and the total number of activities goes up by two.

9.2.1.3.4 New insertion type 4.1, 4.2, 4.3:

For a small group, the biomed activity conflicted with an activity in the AHD which was known to be current as of sweep 6 but whose end date was originally missing and had either been imputed or computed as the start of the N+1 activity. In these cases, it was deemed appropriate to insert the biomedical activity into the sequence starting in the month of sweep 6 interview, but to allow it to run beyond the month of biomedical assessment up until the start date of the N+1 activity (as opposed to truncating them at the date of biomedical assessment). This was for consistency with the

construction of the AHD, where activities with missing end dates were assumed to run until the start of the next activity. If the biomed start date was after sweep 6, it was used as the start date for the new activity and the Nth AHD activity truncated in that month; if the biomed start date was either missing or reported as prior to sweep 6 interview (and therefore definitely incorrect, since the Nth AHD activity was known to be current at that time) the date of biomed interview was used for the start date and the Nth activity truncated then. All activities from the N+1 onwards get bumped up by one, and the total number of activities goes up by one.

Using this final dataset, summary measures of past unemployment were calculated for analysis of outcomes measured at sweep 8, the end point of the original AHD. For investigation of outcomes measured at the biomedical sweep, an additional stage would involve truncation of the updated activity histories at the date of biomedical assessment before appropriate summary measures could be calculated for those analyses.

9.2.2 Appendix D: Construction of a new Activity Histories Dataset for BHPS/UKHLS participants

While for the 1958 Birth Cohort, a version of the activity Histories Dataset was available which I then modified, no such resource was available for the BHPS/UKHLS data. The closest thing was the most recent version of a combined work-life histories database by Halpin[285]. However, this only incorporated information up until year 15 of BHPS, and was constructed using methods which meant it would be very difficult to append new data in a consistent way.

I therefore decided to construct a new dataset of continuous employment histories for each of the participants in the BHPS component of the UKHLS, spanning 20 years for participants present at all waves since 1991. Considering both current activities at all waves and past activities reported at all waves except a participant's first meant that up to 190 activities needed to be considered for each participant.

As with the NCDS AHD a set of core rules were followed, although the nature of the exercise was somewhat different, and the task substantially bigger. With the NCDS AHD, the objective had been to reconcile conflicting and mutually exclusive accounts of activities in a fairly narrow time period. With the BHPS/UKHLS data, the exercise comprised stitching together up to 20 reports of current activities which needed to be reconciled first with one another and then with 19 sets of retrospectively reported activities.

The structure of the data was also very different. In the NCDS, the collection of reports of current and past activities given at sweeps 4-8 had originally contained many duplicate accounts of the same activities (i.e., where a current activity spanned across more than one sweep), with all activities stored in slots relating to the sweep at which they were reported. In the construction of the 2011 version of the NCDS AHD, all duplicates were identified and removed. The remaining non-duplicate activity spells drawn out and re-ordered in 1-34 by their start and end dates. The first and last sweep at which the activity had been mentioned, and whether as current or past, were saved as extra

details. It was to data in this format that I made modifications based on the biomedical sweep information.

In contrast, with the BHPS/UKHLS data I was starting from scratch, and no such reordering had been done. Activity spells were ordered with respect to the timing of the report – one current and up to 10 past spells at each wave. A large part of this task was therefore identifying which of the current reports were duplicates of earlier current reports. I decided that, rather than removing all duplicate activities and reordering the remaining activities in a temporal sequence by start/end dates, I would keep all reports ordered by the date of report, and furthermore keep duplicates in the dataset. Nevertheless, duplicates were flagged to ensure that only one copy would be used to calculate summary measures, and the most reliable start date (the first report, or a modified first report after overlap with a previous current activity had been reconciled) was shifted through the sequence of duplicates from the earliest to the last duplicate in the series, overriding later accounts. Similarly, the end date from the last spell in each series of duplicates, which at earlier reports would have been unknown, was shifted back through to the very earliest of the series of duplicates. In this way, a dataset resulted in which every current report across a 20 year-period had both a start and an end date drawing on the most appropriate information given across the waves. The advantage of this structure, as opposed to the structure of the NCDS AHD, is that it more easily allows analysis of durations from multiple vantage points and will therefore be more user-friendly both for me in future work and for other any other users of this dataset.

Activity histories were set to start of the date of a participants' first interview. This meant that unlike at later waves, past activities from the first wave were not considered, because the lack of a current activity prior to this point meant there was no check on the accuracy of those retrospectively-reported dates.

General principles:

Timing of reports

As with the updating of the NCDS AHD, the trumping principle in this exercise was that current reports take precedence over retrospectively-given reports, and recent retrospective reports over more distant ones. Hence, a start date of a current activity could not be trusted if it conflicted with the account of current activity given at a previous wave, and the first ever report of start date of a current activity reported as current at multiple waves was assumed to be the most reliable.

9.2.2.1.1 Midpoint logic

In every case where an assumption about the exact date of an activity changeover was required, a general principle was applied: where the changeover was known to have occurred between certain limits, it was assumed to have occurred at the midpoint of the possible range. For example, if a current activity lacked a start date but was of a different type to the current activity reported the sweep before and no past activities since then were reported, the changeover was assumed to take place midway between the two interview dates. This logic was also applied where the changeover points between 3 or more activities were unclear, but a start or end date of both the first and the last activity were known. Hence, if a current activity lacked a start date and was of a different type to the current activity reported at the previous sweep, but two past activities also lacking start and end dates had been reported, three changeover points were calculated at equally-spaced intervals between the left and right-hand limit.

An equivalent principle was applied in cases where the year of an activity changeover was known but not the month: June was assumed, since again this is the midpoint of the possible range. A handful of activity spells had seasons codes instead of a month, where the participant could not remember the month but remembered the time of year. The same logic was applied again, such that seasons were recoded to the month in the middle of the season: April for spring, July for summer, October for autumn and January for winter.

9.2.2.1.2 Main/additional activities

A handful of participants had reported past activities which had supposedly occurred while a current activity had been ongoing, indicating they had interpreted the questions about past activities differently to other participants. These past activities were assumed to be additional as opposed to main activities, and removed from the dataset for consistency.

9.2.2.2 Stages of the process

9.2.2.2.1 Filling in gaps

The first stage in the process involved using retrospective accounts from later waves to fill in gaps in the histories at earlier waves. These gaps could be of two types: missing activity type and start date (which occurred where only a proxy interviews had been given), or missing start date but usable activity type (which could occur either where only a proxy interview was given, or where the participant had neglected to fill in the start date). Information from later waves was used to fill in this information if either a current or past activity was later reported to cover the earlier period.

A similar principle was applied to fill in gaps where a participant was entirely absent for a sweep but later re-entered the study. The start date of the earliest activity from the re-entry wave (current activity or the earliest of the past activities where these were reported) was used to fill part of the gap backwards and the current activity from the last sweep before the gap was assumed to run until that point.

9.2.2.2.2 Reconciling discrepancies

The second stage involved sequencing activities which conflicted with each other. If a current or past activity reported at a given wave had a start date prior to a previous year's current activity and was of a different type, the start date of the later activity was shifted forward to start immediately after the earlier wave's interview, removing the overlap. If it was a past activity whose start and end date both preceded the earlier current activity, it was assumed to be an additional activity and dropped entirely.

9.2.2.2.3 Identifying duplicates

If a current activity had a start date prior to a previous year's current activity and was of the same type, they were assumed to be duplicate reports of same activity. Since the start date from the earlier report can be assumed to be more reliable, this was ultimately shifted through all duplicates of the activity until the last in the sequence. Similarly, since only the last in the sequence would have an end date, this was shifted back through all copies of the activity until the first. To facilitate this, all current activities were assigned a code of 0 (not a duplicate, not repeated) 1 (not a duplicate, but will be repeated) 2 (a duplicate, will be repeated) or 3 (last in a series of duplicates), which were also used to calculate summary measures.

For BHPS participants, outcomes of interest were all measured at sweep 3 of UKHLS, 20 years after the first BHPS wave. Summary measures were therefore all calculated using the date of the sweep 3 interview as the end point, except for the biomedical outcomes where an additional period of around 5 months between the mainstage interview and the nurse visit itself was added onto the histories using retrospective information given at wave 4. This was to ensure that activity histories were as complete and accurate as possible at the time of blood sample collection. Again, activities starting and ending in the same month were assigned a duration of 1 month so as to count towards summary measures of unemployment.

9.3 APPENDICES RELATING TO CHAPTER 4: UNEMPLOYMENT AND INFLAMMATION, CROSS-SECTIONAL ANALYSES

9.3.1 Appendix E: Inflammatory markers by year and country (final analytic samples), HSE/SHeS

	CRP (mg/L)		Fibrinogen (g/L)		CRP>3mg/L	
	N	Mean (S.D.)	N	Mean (S.D.) Fibrinogen	N	% CRP>3mg/L
HSE 1998/9	7208	1.93(2.02)	6669	2.52(0.60)	7208	21.2
HSE 2003	5499	2.04 (2.07)	4910	2.82(0.64)	5,499	23.5
HSE 2006	4847	1.97(2.00)	4268	2.86(0.63)	4847	21.9
HSE 2009	1443	2.00(1.98)	1277	2.98(0.52)	1443	22.8
SHeS 2003	2498	2.04(2.09)	2191	2.84(0.61)	2498	22.7
SHeS 2008	508	2.07(1.99)	431	3.13(0.49)	508	24.0
SHeS 2009	518	2.01 (1.99)	435	3.02(0.59)	518	21.8
SHeS 2010	504	1.81 (1.84)	433	2.86(0.51)	504	18.3
ALL ENGLISH SURVEYS	18997	1.98(2.03)	17202	2.73(0.64)	18997	22.2
ALL SCOTTISH SURVEYS	4028	2.01(2.03)	3522	2.90(0.60)	4028	22.2

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